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Formaldehyde Dialkylhydrazones as Neutral Formyl Anion and Cyanide Equivalents: Nucleophilic Addition to Conjugated Enones

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A versatile methodology for the nucleophilic formylation and cyanation of conjugated enones is reported. The procedure is based on the use of formaldehyde dimethylhydrazone, which, acting as a *neutral* formyl anion equivalent, adds to preformed trialkylsilyl−enone complexes. Both 4-(silyloxy)-3-enal hydrazones **3** or deprotected 4-oxo aldehyde monohydrazones **4** can be obtained as products depending on quenching conditions. In full analogy, an asymmetric version of the reaction using chiral formaldehyde SAMP-hydrazone as a neutral synthon of the *chiral formyl anion* has been developed, giving rise to the corresponding adducts **5** and **6** in good yields and with excellent diastereoselectivities (de 85−≥98%). Ozonolysis or HCl-mediated hydrolysis of adducts **4** and **6** readily affords racemic and optically enriched 4-oxo aldehydes **7**, respectively. Additionally, high-yielding MMPP-oxidative cleavage of 4-oxo hydrazones **4** and **6** has been performed to obtain 4-oxo nitriles **8** in racemic and optically enriched forms, respectively. In this way, interesting chiral bifunctional building blocks, some of them bearing newly created stereogenic quaternary centers, have been efficiently synthesized.

Introduction

The Michael addition of carbon nucleophiles to conjugated enones is one of the most powerful methods for carbon−carbon bond formation.[1] Depending on the functionality present on the nucleophile, many different families of compounds have been synthesized using this tool. Thus, the introduction of nonfunctionalized fragments yielding higher ketones involves the addition of organometallics (most usually cuprates) and has been optimized in order to minimize competing side reactions, such as 1,2-addition to the carbonyl group. Likewise, efficient methodologies for the introduction of enolates and aza enolates have been reported for the synthesis of several kinds of 5-oxo carbonyl compounds. There is also literature on the conjugate addition of acyl anion equivalents as nucleophiles,[2,3] leading, after release of the masked carbonyl group, to 1,4-diketones. During the last few years, the need for optically pure compounds has invoked considerable activity directed toward the development of methodologies for carrying out all these reactions in an enantioselective way.[4] Thus, the asymmetric introduction of alkyl chains into the enone skeleton (→ higher ketones) has been satisfactorily accomplished by addition of several kinds of organometallics,[5] using both chiral ligands or catalysts as the source of chirality. Likewise, many optically enriched 1,5-bifunctionalized compounds have been synthesized from enones by asymmetric addition of silyl enol ethers,[6] enamines,[7] imines,[8] malonates,[9] aminocarbene complex anions,[10] and other enolate and aza enolate equivalents. For the asymmetric Michael addition of acyl anion equivalents to prochiral enones (→ 1,4 dicarbonyl compounds), the number of possibilities available is rather limited.[11]

As a particular case, the conjugate nucleophilic formylation (→ 4-oxo aldehydes) is of special significance due to the synthetic versatility of the formyl group. There-

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⊗ Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Pergamon: Oxford, 1992. (b) Lee, V. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 4, Chapters 1.2 and 1.3. (c) Kozlowski, J. A. *Ibid.* Vol. 4, Chapter 1.4.

(2) (a) Ager, D. J. In *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*; Hase, T. A., Ed.; Wiley: New York, 1987; pp 19−72. (b) Dondoni, A. *Advances in the Use of Synthons in Organic Chemistry*; JAI Press Ltd.: London, 1993; pp 2−28. (c) Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 2143. See also references cited therein.

(3) Particularly related to this work is the ene-type thermal addition of certain aldehyde monoalkylhydrazones with unhindered acceptors such as methyl acrylate and acrylonitrile: (a) Baldwin, J. E.; Adlington, R. M.; Bottaro, J. C.; Jain, A. U.; Kolhe, J. N.; Perry, M. W. D.; Newington, I. M. *J. Chem. Soc., Chem. Commun.* **1984**, 1095. (b) Baldwin, J. E.; Adlington, R. M.; Jain, A. U.; Kolhe, J. N.; Perry, M. W.D. *Tetrahedron* **1986**, *42*, 4247. The reaction with more-substituted substrates and with conjugated enones, however, has not been reported.

(4) Recent reviews: (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochemi.* **1989**, *20*, 87. (b) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *20*, 227.

(5) Review: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. Recent examples: Wang, Y.; Gladysz, J. A. *J. Org. Chem.* **1995**, *60*, 903 and references cited therein.

(6) Lohray, B. B.; Zimbiniski, R. *Tetrahedron Lett.* **1990**, *31*, 7273.

(7) Hickmott, P. W. In *The Chemistry of Enamines*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1994; p 727.

(8) (a) Desmaële, D.; Pain, G.; d'Angelo, J. *Tetrahedron: Asymmetry* **1992**, *3*, 863. (b) For a review, see: d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron: Asymmetry* **1992**, *3*, 459.

(9) (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571. (b) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1176. (c) Kawara, A.; Taguchi, T. *Tetrahedron Lett.* **1994**, *35*, 8805.

(10) Anderson, B. A.; Wulff, W. D.; Rahm, A. *J. Am. Chem. Soc.* **1993**, *115*, 4602.

(11) For a leading reference see: Enders, D.; Kirchhoff, J.; Mannes, D.; Raabe, G. *Synthesis* **1995**, 659.

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fore, much effort has been focused on the development of appropriate umpoled reagents, which are based almost exclusively on the anionic[12] forms derived from two types of compounds: (i) those of the general structure XCH_2Y, where X and/or Y are anion-stabilizing functions, and (ii) those derived from X(Y=)CH structures, which require a subsequent reduction step for the regeneration of the carbonyl function. These approaches, however, gave satisfactory solutions only in a limited number of cases and are in general subject to various limitations. Among these, the most common are the need for strong bases for generating the actual anionic formyl equivalent, the lack of selectivity observed for substrates containing multiple electrophilic centers, the lack of reactivity toward β,β-disubstituted substrates, and the difficulties encountered in many cases regarding the release of X and Y to regenerate the carbonyl function, in particular the need to use environmentally undesirable mercury salts or strongly acidic conditions. A survey of the literature reveals that no efficient enantioselective formylating protocols have been described up to now.[13] This surprising finding reflects in most cases the unavailability of chiral forms of the formylating reagents referred to above and sometimes the inefficiency and/or lack of selectivity of the process. Thus, an efficient general method for the nucleophilic formylation of enones is still a challenge, particularly if an enantioselective version (a practically unprecedented reaction) is to be developed.

In this context, we have explored the synthetic possibilities of dialkylhydrazones, whose aza enamine character should theoretically make them behave as nucleophilic acylating reagents in the same way as enamines do.[7] Such reactivity has been exhibited in the reactions of aldehyde dialkylhydrazones with strong electrophiles such as the Vilsmeier reagent,[14] sulfonyl isocyanates,[15] highly reactive Mannich bases,[16] and trifluoroacetic anhydride,[17] but it is in fact too low for the reaction with weaker electrophiles such as carbonyl compounds[18] or Michael-type acceptors. On the other hand, we have recently reported some results on the use of *formaldehyde* dialkylhydrazones (FDAH's) as *neutral* formyl anion equivalents, which have proved to be a good alternative to the existing methodologies. Thus, their addition reaction to compounds containing reactive double bonds such as conjugated nitroalkenes[19] and to activated carbonyl compounds such as α-alkoxy aldehydes[20] successfully gave rise, after release of the masked carbonyl function, to the corresponding formylated products. We now wish to report in full the trialkylsilyl triflate-promoted conjugate addition of formaldehyde dimethylhydrazone (**1a**, Figure 1) to α,β-unsaturated ketones, the asymmetric version of this reaction using the SAMP-derived hydrazone (**1b**) as an efficient *chiral, neutral* formyl anion equivalent,[21] and the synthesis of racemic and optically enriched 4-oxo aldehydes and 4-oxo nitriles from the obtained adducts.

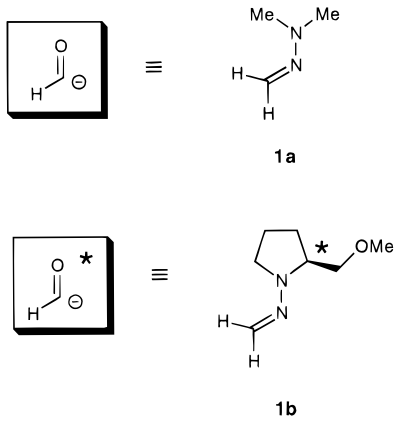


Figure 1.

Results and Discussion

Addition of Formaldehyde Dimethylhydrazone to Conjugated Enones. The preliminary experiments carried out using readily available[17a] formaldehyde dimethylhydrazone (FDMH, **1a**) indicated that, in contrast to the related addition to the more electrophilic nitroalkenes[19] or activated aldehydes,[20] the reactivity of hydrazone **1a** was not high enough to generate spontaneous addition to a variety of conjugated enones (**2a**−**i**, Chart 1). Therefore, the presence of a catalyst or promoter was suggested, and several Lewis acids of different strengths ($TiCl_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, etc.), in both catalytic and stoichiometric amounts, were unsuccessfully tested for the activation of the conjugate acceptor. As could be anticipated, the competing irreversible formation of hydrazone−Lewis acid complexes, which readily decomposed as demonstrated in blank experiments, was observed even at low temperatures and constituted a major point of difficulty. Fortunately, this problem could be finally solved by using *bulky* trialkylsilyl [TBDMS or dimethyl(1,1,2-trimethylpropyl)silyl (TDS)] triflates as promoters,[22] giving rise to the formation of the desired adducts trapped as their corresponding silyl enol ethers **3** (Scheme 1). This strategy even allowed the direct addition of the promoter to the mixture of reactants (method B for the synthesis of compounds **3**, see Experimental Section), since the decomposition of the hydrazone **1a** in the presence of the promoter seems to take place

(12) (Trimethylsilyl)thiazole, a formyl anion equivalent belonging to a different class of formyl anion equivalents due to its *neutral* character, has never been reported to behave as such an equivalent in Michael-type reactions.

(13) Some chiral formyl anion equivalents have been tested in their reactions with aldehydes: Colombo, L.;. Di Giacomo, M.; Brusotti, G.; Delugu, G. *Tetrahedron Lett.* **1994**, 35, 2063 and references cited therein. See also ref 2. However, the only attempt described for the addition to enones was using a mono-*S*-oxidized dithioacetal derived reagent and resulted, after a complicated two-step deprotection sequence, in poor yields and low ee values of the corresponding adducts. (a) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *Synthesis* **1981**, 74. (b) Colombo, L.; Gennari, C.; Resnati, G.; Scolastico, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1284.

(14) Brehme, R. *Chem. Ber.* **1990**, *123*, 2039.

(15) Brehme, R.; Nikolajewski, H. E. *Tetrahedron Lett.* **1982**, *23*, 1131.

(16) Brehme, R.; Nikolajewski, H. E. *Tetrahedron* **1976**, *32*, 731.

(17) (a) Kamitori,Y.; Hojo, M.; Masuda, R.; Fujitani, T.; Ohara, S.; Yokohama, T. *J. Org. Chem.* **1988**, *53*, 129. (b) Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T.; Ohara, S.; Yamada, K.; Yoshikawa, N. *J. Org. Chem.* **1988**, *53*, 519.

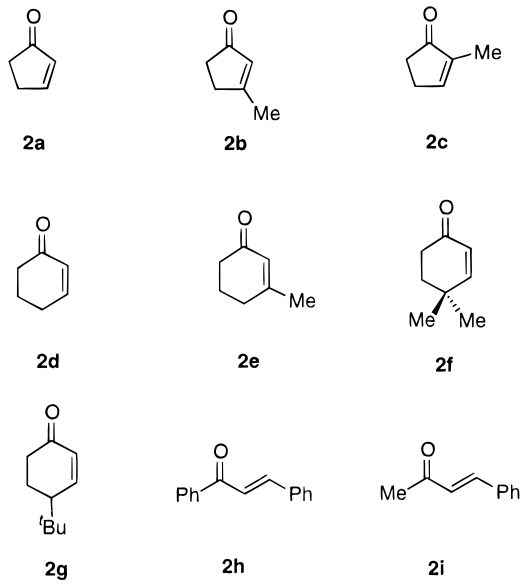
(18) The *intramolecular* addition of the azomethine carbon of aromatic hydrazones to a neighbor carbonyl group has been reported: Shen, J.-K.; Katayama, H.; Takatsu, N.; Shiro, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2087. The authors also reported failed attempts to perform the same reaction intermolecularly.

(19) (a) Lassaletta, J. M.; Fernández, R. *Tetrahedron Lett.* **1992**, *33*, 3691. (b) Lassaletta, J. M.; Fernández, R.; Gasch, C.; Vázquez, J. *Tetrahedron* **1996**, *52*, 9143. (c) Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Tetrahedron Lett.* **1994**, *35*, 471. (d) Enders, D.; Syrig, R.; Raabe, G.; Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Synthesis* **1996**, 48. (e) Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M. *Synthesis* **1996**, 627.

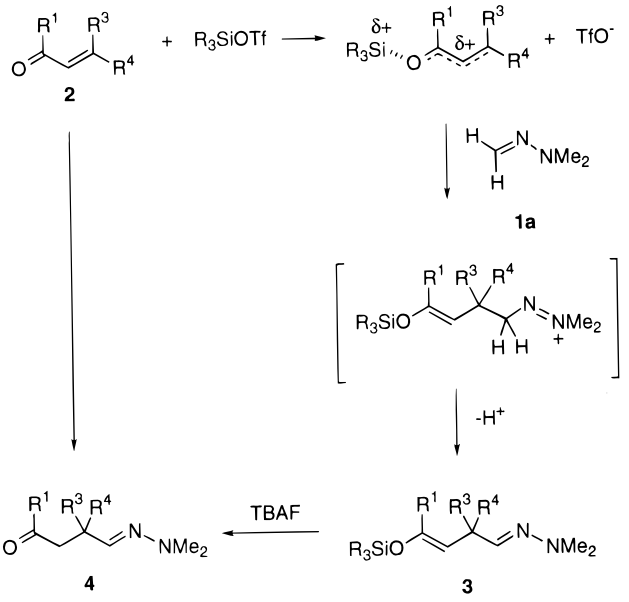
(20) Lassaletta, J. M.; Fernández, R.; Martín-Zamora, E.; Pareja, C. *Tetrahedron Lett.* **1996**, *37*, 5787.

(21) A preliminary account of this work has recently appeared: Lassaletta, J. M.; Fernández, R.; Martín-Zamora, E.; Díez, E. *J. Am. Chem. Soc.* **1996**, *118*, 7002.

Chart 1

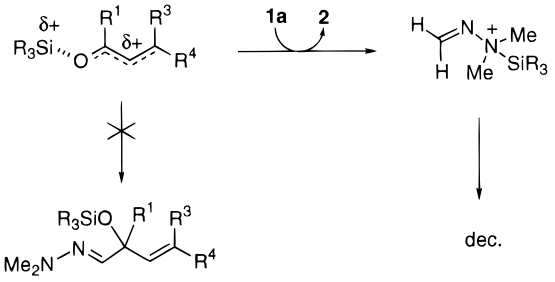


Scheme 1



at a slower rate than the fast addition reaction. Presumably, the great steric hindrance around the chosen promoter makes the complexation of the small carbonylic oxygen on ketone **2** much easier than that of the dialkyl-substituted nitrogen on the hydrazone moiety. Conditions B were used in some cases to avoid the competing spontaneous silylation of the enolic forms of some of the starting enones. Nevertheless, consumption of the starting enone **2** because of this side reaction was insignificant in most cases, and better results were generally observed when the hydrazone **1a** was added slowly to a solution of preformed trialkylsilyl enone complexes (method A for the synthesis of compounds **3**, see Experimental Section). A screening of reaction conditions revealed little influence of the solvent, while optimal yields were observed for reactions carried out at temperatures around 0 °C using a 1:1.1:1.5 enone:promoter:hydrazone ratio. TLC control

Scheme 2



indicated total consumption of the starting enone in most cases, but relatively high amounts of unreacted material were recovered when sterically hindered substrates, such as 4-*tert*-butylcyclohexenone (**2g**) (33% unreacted) and 4,4-dimethyl-3-cyclohexenone (**2f**) (4% unreacted), were used as substrates. As the quantitative formation of the enone-promoter complexes is assumed under conditions A, its recovery may well be attributed to a partial irreversible transfer of the trialkylsilyl group from the complex to the amino nitrogen atom in the hydrazone (Scheme 2). The reaction proceeded cleanly in all cases, and the ^{1}H NMR analysis of the crude indicated the absence of 1,2 adducts, as was expected taking into account the neutral and extremely soft character of the nucleophile, on one hand, and the great steric hindrance around the carbonyl group due to chelation with bulky trialkylsilyl groups, on the other. In addition to the already mentioned survival of the hydrazone, the anticipated regioselectivity constitutes a second reason for the choice of such sterically demanding reagents. The rich chemistry of silyl enol ethers makes the primary adducts **3** appear to be promising synthetic intermediates that can be used not only as protected forms of the corresponding ketones but also for further transformations as the regioselective introduction of diverse functionalities at C-2.[23] Although the low boiling points of compounds **3** made their isolation in good yields from small-scale reactions difficult in some cases, they were mostly stable compounds and could be purified by column chromatography and used for further reactions. Moreover, the corresponding deprotected adducts **4** could also be alternatively obtained in a "one pot" operation by simply quenching the reaction mixtures with tetrabutylammonium fluoride (TBAF), which, in order to avoid an excess of triflic acid, must equal the initial amount of promoter added to the reaction mixture. Verifying the generality of the addition reaction, many different kinds of enone were successfully examined as substrates. Thus, five- (entries **a** and **b**) and six-membered (entries **d**, **f**, and **g**) cyclic enones, as well as acyclic ones (entries **h** and **i**), afforded the corresponding adducts **3** and **4** in moderate-to-good yields. The results for the synthesis of compounds **3** and **4** are collected in Table 1.

Addition of SAMP-Derived Formaldehyde Hydrazone 1b to Prochiral Conjugated Enones. Having the optimal conditions for the addition reaction in the racemic series established, studies were directed toward an asymmetric version of the reaction based on the use of a chiral formaldehyde hydrazone. To this end,

(22) For other trialkylsilyl-promoted conjugated additions of soft carbon nucleophiles to enones see: (a) Kim, S.; Park, J. H. *Synlett* **1995**, 163. (b) Eriksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182. (c) Katritzky, A. R.; Soloducho, J.; Musgrave, R. P.; Breytenbach, J. C. *Tetrahedron Lett.* **1995**, *31*, 5491.

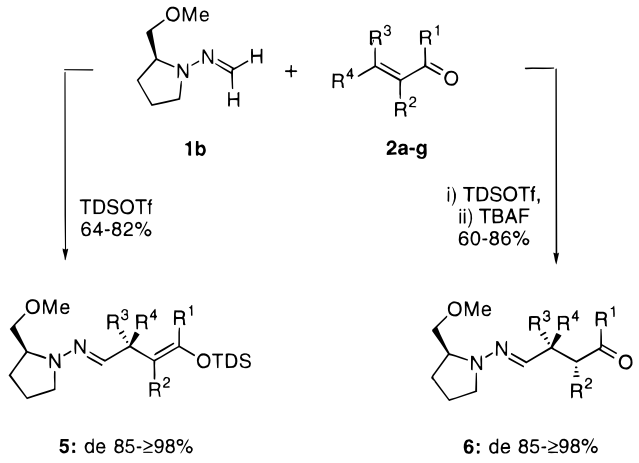
(23) Following well-established procedures, this position could be alkylated, used as nucleophile in the Mukaiyama aldol reaction, or hydroxylated (the Rubottom reaction). Additionally, a recently reported reaction describes the introduction of a nitrogenated function in this position: Du Bois, J.; Hong, J.; Carreira, E. M.; Day, M. W. *J. Am. Chem. Soc.* **1996**, *118*, 915.

Table 1. Synthesis of 4-(Silyloxy) 3-Enal Dimethylhydrazones 3 and 4-Oxo Dimethylhydrazones 4

enone **2**	promoter	method	workup	product	yield (%)
2a	TDSOTf	A	TBAF	**4a**	72
2a	TDSOTf	A	$NaHCO_3$	**3a**	*a*
2a	TBDMSOTf	A	$NaHCO_3$	**3a′**	*a*
2b	TDSOTf	A	TBAF	**4b**	91
2d	TDSOTf	A	$NaHCO_3$	**3d**	*a*
2d	TBDMSOTf	A	$NaHCO_3$	**3d′**	*a*
2d	TDSOTf	A	TBAF	**4d**	75
2f	TDSOTf	A	$NaHCO_3$	**3f**	60
2f	TDSOTf	A	TBAF	**4f**	65[b]
2g	TDSOTf	B	$NaHCO_3$	*cis*-**3g**	52[c]
2g	TBDMSOTf	B	TBAF	*cis*-**4g**	55[d]
2h	TDSOTf	B	$NaHCO_3$	**3h**	50
2h	TBDMSOTf	B	$NaHCO_3$	**3h′**	58
2h	TDSOTf	B	TBAF	**4h**	68
2i	TDSOTf	A	TBAF	**4i**	55

[a] Not determined (see text). [b] 4% of **2f** recovered. [c] 30% of **2g** recovered. [d] 33[c]% of **2g** recovered.

Scheme 3



(−)-(*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) was chosen as a convenient, inexpensive chiral hydrazine for the preparation of the reagent. Thus, SAMP-derived formaldehyde hydrazone **1b**[19c,d] was made to react with a variety of prochiral enones **2** previously activated by means of TDSOTf; this procedure gave rise, in full analogy to the foregoing FDMH reaction, to the corresponding diastereomeric silyl enol ethers **5**, which, in contrast to the FDMH-derived adducts, could be easily isolated.[24] Likewise, the SAMP-derived 4-oxohydrazones **6** were isolated in "one pot" by quenching in the presence of TBAF (Scheme 3). Thus, both classes of adduct could be obtained in satisfactory yields and with an excellent degree of stereoselectivity.[25] Representative experiments for the synthesis of compounds **5** and **6** are collected in Table 2.

It should be stressed that the reactivity exhibited by the SAMP-derived formaldehyde hydrazone **1b** was clearly higher than that of the acyclic dimethylhydrazone **1a**. This effect can be explained considering the presence of the pyrrolidine ring in the reagent, which, as occurs for the related enamines,[26] confers higher π-donor capacity to the aminic lone pair and, therefore, higher nucleophilicity to the azomethine carbon atom. Hence, very fast

Table 2. Synthesis of 4-(Silyloxy) 3-Enal SAMP Hydrazones 5 and 4-Oxo Dimethylhydrazones 6

enone **2**	R^1	R^3	R^2	R^4	product **5** (%)	product **6** (%)	de[a] (%)	confgn
2a	$-(CH_2)_2-$		H	H	64	69	95	*R,S*
2b	$-(CH_2)_2-$		H	Me	76	80	≥98	*R,S*
2c	$-(CH_2)_2-$		Me	H	77	83[b]	97	*R,R,S*
2e	$-(CH_2)_3-$		H	Me	82	86	85	*R,S*
2f	$-(CH_2)_2CMe_2-$		H	H	74	79	94	*S,S*
2h	Ph	H	H	Ph	75	76	≥98	*R,S*
2i	Me	H	H	Ph	c	60	95	*R,S*

[a] See ref 25. [b] 95:5 mixture of *cis* and *trans* isomers. [c] Unstable compound.

reactions were observed even at temperatures as low as −78 °C, provided that the choice of THF as solvent avoids the solubility problems observed when ether or dichloromethane was used instead. As a consequence, the diastereoselectivity of the reaction, which during preliminary experiments proved to be strongly dependent on the temperature, could be improved to excellent levels. As an illustrative example, the diastereoselectivity observed for the synthesis of compound **6b** rose from de 50% when the reaction was carried out at 0 °C to de 73% at −20 °C and finally to de >98% at −78 °C. As the observed diastereoselectivities were not greatly affected by the temperature of quenching (i.e., identical de values were measured for a reaction performed and quenched at −78 °C and for a parallel reaction allowed to warm before quenching), it may be deduced that the reaction is essentially irreversible and that kinetically controlled products are obtained. Interestingly, the reaction also proceeded with similar results in the presence of equimolecular amounts of triethylamine. Under these conditions, any trace of triflic acid eventually formed in the reaction mixture would be neutralized, and theoretically the use of acid-sensitive starting materials should be allowed.

As illustrated in the additions to β,β-disubstituted enones **2b** and **2e**, the possibility of synthesizing compounds containing *all-carbon, quaternary* carbon atoms (bearing four differently functionalized alkyl chains), maintaining a high degree of diastereoselectivity, enhances the synthetic value of this reaction, since such centers are commonly encountered in a variety of natural products, and the range of methodologies for their generation is one of the most restricted in organic synthesis.[27] It should also be mentioned that the proline-derived chiral auxiliary used is available in both enantiomeric forms,[19e] thereby opening access to any desired configuration.

Cleavage of the Hydrazone Moiety. In order to demonstrate the announced synthetic equivalence of FDAHs with the formyl anion, the optimization of the cleavage of the hydrazones to aldehydes was considered a priority. Again, FDMH-derived adducts **4** were first used as a useful model for this transformation, and as expected, they could be easily deprotected by ozonolysis (method A, see Experimental Section) and/or HCl-mediated hydrolysis in a two-phase system (method B), affording the 4-oxo aldehydes **7** in excellent yields (Scheme 4, Table 3). Alternative methods, such as the copper-assisted hydrolysis[28] or other described oxidative

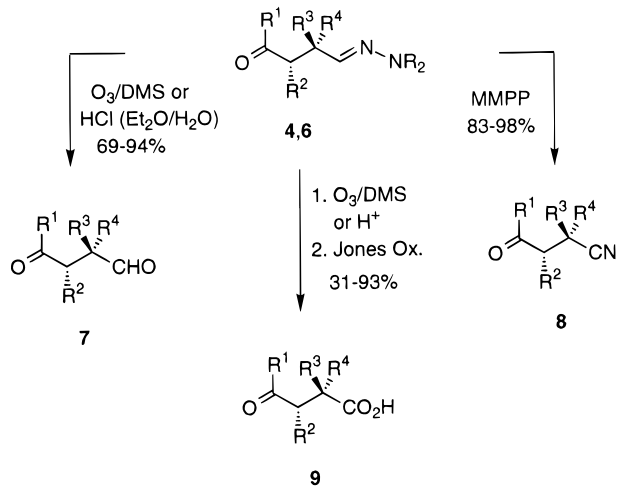
(24) These silyl enol ethers containing the SAMP moiety had much higher boiling points than the parent FDMH-derived adducts, and their stability was adequate for chromatographic purification except for the 4-phenylbutenone-derived compound **5i** (see Experimental Section).

(25) The diastereomeric ratio was determined by ^{13}C and ^{1}H NMR spectroscopy. The de values obtained before chromatography were identical with those for the isolated diastereomeric mixtures.

(26) Häfelinger, G.; Mack, H.-G. In *The Chemistry of Enamines*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: New York, 1994; pp 1−85.

(27) The asymmetric creation of quaternary carbon centers has recently been reviewed: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

Scheme 4



cleavages of the C=N bond,[29] gave no positive results in our hands. Although ozonolysis of the more complex SAMP-derived hydrazones is known to be a rather unpredictable reaction,[30] it proved to be suitable also for compounds **6**, and the desired aldehydes were obtained after the usual workup in good-to-excellent yields. Hydrolysis by HCl, however, led to slightly higher yields of aldehydes **7** from both dimethyl- and SAMP-hydrazones **4** and **6**, as illustrated in several examples (Table 3, entries 9, 10, and 14). Hence, ozonolysis remains as an appropriate alternative for acid-sensitive or racemizable substrates. The rather unstable and volatile aldehyde **7a** was best oxidized *in situ* by treatment of the resulting crude ozonolyzate or hydrolyzate with the Jones reagent to afford the known carboxylic acid **9a**[31] (93% from **4a** *via* ozonolysis; 84% from **6a** *via* HCl-mediated hydrolysis). Compounds **6c**, **4d**, **6e**, **6f**, and **6h** were treated a similar way, affording the corresponding carboxylic acids **9c**−**f**, **h** (Scheme 4, Table 3). Although the absence of racemization under the conditions used for the ozonolysis of similar compounds is a well-documented fact, independent evidence for it was obtained in some cases. Thus, the optical purity of compound **7f** was determined by ^{1}H NMR shift experiments using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as cosolvent and with the help of the racemic form obtained from **4f** and proved to be comparable (ee 95%) with that of the parent adduct **6f** (de 94%). Additionally, two samples of compound **7f**, obtained from compound **6f** by ozonolysis and HCl-mediated hydrolysis, respectively, showed matching $[\alpha]_D$ values, suggesting both reactions to be racemization-free processes. A second piece of evidence was indirectly deduced from the optical rotation data observed for derivative **9a** (obtained by tandem ozonolysis-oxidation of adduct **6a**), which indicated a high optical purity by comparison with literature data.[31]

The synthetic versatility of the dialkylhydrazone moiety could be additionally exploited by demonstrating its equivalence with the cyano group. For this transformation, our recently reported oxidative cleavage of aldehyde dimethylhydrazones **4** by means of magnesium monoperoxyphthalate hexahydrate (MMPP·6H$_2$O)[32] again proved to be an efficient method, affording racemic nitriles **8** in essentially quantitative yields. Comparable yields of the optically enriched nitriles **8** were obtained when the SAMP-derived hydrazones **6** were exposed to the same treatment. In order to confirm the already reported[19d,e] absence of racemization during this process, independent ee measurements were carried out in some cases. Thus, the optical purity of compounds **8h** and **8i** was verified by ^{1}H NMR analysis using Eu(hfc)$_3$ as the chiral lanthanide shift reagent. To this aim, the corresponding racemic compounds, obtained from dimethylhydrazones **4h** and **4i**, were used as references. Additionally, the optical purities of compounds **8a**, **8e**, and **8f** were indirectly established using (2*R*,3*R*)-2,3-butanediol as a chiral derivatizating reagent. Therefore, the corresponding diastereomeric ketals **10** were easily prepared under established conditions (Scheme 5), and their optical purities were determined by ^{13}C NMR. The results for the synthesis of derivatives **7**−**9** are summarized in Table 3.

Determination of Absolute Configurations and Stereochemical Aspects. The assignment of the configuration of the newly created stereogenic centers was made in several cases. First, the absolute configuration of the crystalline (*R*,*S*)-**6h** (an open-chain compound) was unequivocally determined by X-ray structure analysis,[33] while that corresponding to **6i** was assigned by analogy, taking into account the close relationship between the two structures. A chemical correlation allowed the assignment of the absolute configuration corresponding to **6a**: comparison of the optical rotation of the derived (+)-(*R*)-3-oxocyclopentanecarboxylic acid [(*R*)-**9a**] with literature data[31] led to the assigned *R*,*S* configuration. Again, structurally related cyclopentenone-derived adducts **6b** and **6c** were deduced to be 3*R* by analogy. For the determination of the absolute configuration of the six-membered adduct **6f**, a well-established empirical rule developed by Lemière *et al.*[34] was the method of choice. Hence, the mixture of (2*R*,3*R*)-2,3-butanediol-derived ketals **10f** (Figure 2) showed in its ^{13}C NMR spectrum two sets of peaks in a 97:3 ratio (selected shifts shown in Table 4). These two sets of peaks were confirmed as corresponding to the two diastereoisomers, since they were also found in a 1:1 ratio when racemic **8f** was used for the synthesis of ketal **10f**. According to the rule, the 3*S* configuration was then assigned to the major isomer **10f**.[35] For the determination of the absolute configuration of compound **6e**, a similar analysis was made for the corresponding ketal **10e**. The conformational requisite

(28) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, *41*, 3667.

(29) (a) Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3; (b) **1976**, 11. (c) Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7.

(30) Failure of the ozonolysis of SAMP-derived hydrazones in other systems has forced the synthesis of the aldehydes *via* reduction of the easily available nitriles: (a) Enders, D.; Backhaus, D.; Runsink, J. *Tetrahedron* **1996**, *52*, 1503. (b) Fernández, R.; Martín-Zamora, E.; Pareja, C.; Vázquez, J.; Lassaletta, J. M. Unpublished results. However, ozonolysis is particularly convenient since the chiral auxiliary (SAMP) can be recycled: Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.

(31) (*R*)-**9a** had $[\alpha]^{21}_D$ +21.8° (*c* 1.9, CH$_3$OH). The maximum reported value for this compound is $[\alpha]^{21}_D$ +22.1° (*c* 1.9, CH$_3$OH): (a) Toki, K. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 333. (b) Sato, Y.; Nishioka, S.; Yonemitsu, O.; Ban, T. *Chem. Pharm. Bull.* **1963**, *11*, 829.

(32) Fernández, R.; Gasch, C.; Lassaletta, J. M.; Llera, J. M.; Vázquez, J. *Tetrahedron Lett.* **1993**, *34*, 141.

(33) Complete crystallographic details for this compound will be published separately: Diánez, M. J.; Estrada, M. D.; López-Castro, A.; Pérez-Garrido, S., Dpto. Física Materia Condensada, Apartado de Correos 1065, E-41080 Seville, Spain.

(34) Lemière, G. L.; Dommisse, R. A.; Lepoivre, F. C.; Alderweireldt, F. C.; Hiemstra, H.; Wynberg, H.; Jones, J. B.; Toone, E. J. *J. Am. Chem. Soc.* **1987**, *107*, 1363.

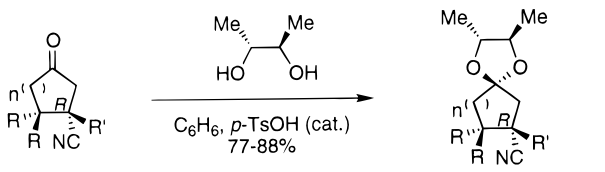
(35) The *S* configuration at the newly created center in this case is simply the result of a change in CIP priorities; the stereochemistry, however, is homogeneous with that observed for the rest of the additions and in accordance with a uniform reaction pathway.

Table 3. Synthesis of 4-Oxo Aldehydes 7, 4-Oxo Nitriles 8, and 4-Oxo Carboxylic Acids 9

entry	starting compd	product **7** % yield	product **7** $[\alpha]^{22}_D$	product **7** ee	product **8** % yield	product **8** $[\alpha]^{22}_D$	product **8** ee	product **9** % yield	product **9** $[\alpha]^{22}_D$	product **9** ee	confgn
1	**4a**	*a*			91			93			
2	**6a**	*a*			90	+35.3	93[b]	84	−21.8[c]	99[d]	*R*
3	**4b**	85[e]			86						
4	**6b**	87[e]	−22.0	>98[f]	98	−54.2	>98[f]				*R*
5	**6c**	94[g]	+82.3	97[f]	70	+63.6	97[f]	28	+66.6	97[f]	*R,R*
6	**4d**	*a*			91			92			
7	**6e**	69[e]	+5.5	85[f]	87	−24.3	84[b]	46	−14.0	85[f]	*R*
8	**4f**	71[e]			91						
9	**6f**	69[g]	+34.1	95[h]	83	−11.7	94[b]	64	+18.8	94[f]	*S*
	6f	78[e]	+34.3								
10	**4g**	75[g]			86						
	4g	81[e]									
11	**4h**	88[e]			90						
12	**6h**	79[g]	−55.6[i]	*j*	95	+15.3	>98[k]	31	−92.9	>98	*R*
13	**4i**	75[e]			91						
14	**6i**	72[g]	−39.7[i]	*j*	91	+8.1	96[k]				*R*
	6i	88[e]	−41.6[i]								

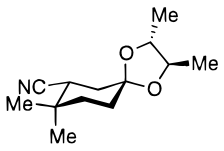
[a] Unstable compound. [b] Determined as de of its (2*R*,3*R*)-2,3-butanediol derived ketal **10**. [c] See ref 31. [d] Determined by comparison with the reported data. [e] Obtained by HCl-mediated hydrolysis. [f] Given as diasteromeric excess of compounds **6**. [g] Obtained by ozonolysis. [h] Determined by shift experiments using (*R*)-1-(9-anthryl)-2,2,2-trifluoroethanol as cosolvent. [i] Maximum values measured for freshly obtained products. [j] Racemization occurs during ee determination with $Eu(hfc)_3$. [k] Determined by shift experiments using $Eu(hfc)_3$ in $CDCl_3$.

Scheme 5

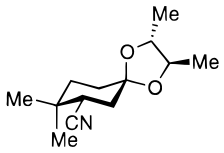


8a: n=1, R=R'=H
8e: n=2, R=H, R'=Me
8f: n=2, R=Me, R'=H

10a: n=1, R=R'=H
10e: n=2, R=H, R'=Me
10f: n=2, R=Me, R'=H

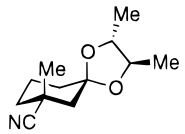


(3*R*)-**10f**

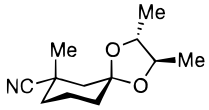


(3*S*)-**10f**

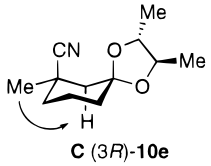
Figure 2.



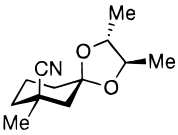
A (3*R*)-**10e**



B (3*S*)-**10e**



C (3*R*)-**10e**



D (3*S*)-**10e**

Figure 3.

Table 4. Selected ^{13}C NMR Chemical Shifts Used for the Assignment of the Absolute Configuration of f- and e-Series Compounds

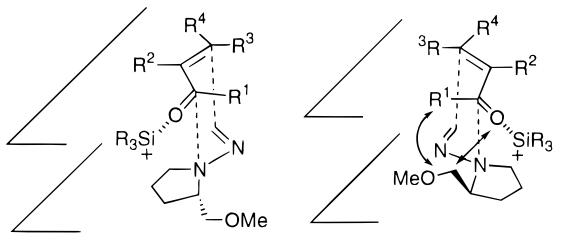
compd	isomer	δC-2	δC-3	δC-5	δC-6	assigned to
10f	major	35.2	37.8	35.7	32.5	3*S*[a]
10f	minor	36.1	37.4	36.2	31.7	3*R*[a]
10e	major	45.9	33.5	20.6	35.4	**B** or **C**[b]
10e	minor	44.8	33.8	20.4	36.1	**A** or **D**[b]

[a] See Figure 2. [b] See Figure 3.

for the application of the rule, i.e., a chairlike geometry of the ring, was first confirmed by means of two "W" coupling constants [$^4J_{H-2eq,H-6eq} \cong {}^4J_{H-2eq,H-4eq} \cong 1.9$ Hz] observed in its ^1H NMR spectrum. As the axial−equatorial disposition of the methyl and cyano groups cannot be assumed considering steric factors as in the preceding case, two different conformers for each diastereoisomer should be considered (Figure 3, forms **A**−**D**). Consequently, the use of the rule indicated only that the position of the C-3 quaternary center relative to the dioxolane moiety was that of forms **B** or **C**, according to the analysis of the selected ^{13}C NMR chemical shifts shown in Table 4. The equatorial orientation of the methyl group at C-3 (hence, the assignment of the 3*R*-configuration to this compound) was then demonstrated by means of a NOE difference experiment, which showed the specific enhancement depicted for isomer **C** (Figure 3). Additionally, a gated ^{13}C NMR spectrum was recorded, which showed no estimable *anti* $^3J_{C,H}$ coupling constants for the methyl carbon atom, while the peak corresponding to the axial CN carbon was clearly broadened because of these couplings. Assuming retention of configuration at the new chiral center along the route **6** → **10**, the *S* and *R* configurations can be assigned to any compound belonging to series **f** and **e**, respectively. The C-2/C-3 relative stereochemistry of **c**-series compounds has been assigned to be *cis* by comparison of the physical data of both the racemic derived nitrile (±)-**8c** and its optically enriched form (*R*)-**8c** with those previously reported for the racemic form.[36] Finally, it is noteworthy that the addition of hydrazone **1a** to the sterically-hindered, 4-substituted enone **2g** yielded a single product, whose stereochemistry, as for all **g**-series compounds, was assigned *cis* by comparison of the derived nitrile **8g** with reported data.[37]

Interestingly, the results outlined above indicate that the nucleophilic attack always occurs on the same face

(36) Cocker, W.; Grayson, D. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1153.



I **II**

Figure 4.

of the enone, irrespective of its structure and the geometry of the double-bond. As a direct consequence, *the stereochemistry of the obtained products can be predicted* for additions to any enone not having structural features different from those studied here. As an explanation of these findings, a cyclic, compact, chairlike geometry for the approach of the reactants is proposed (Figure 4). Thus, the steric repulsion between the CH_2OMe group in the pyrrolidine ring and both the highly demanding TDS^+-chelated oxygen atom and the substituent R^1 should result in a much higher energy for **II** than for **I**, according to the absolute configuration and the high induction observed. This compact geometry, stabilized by secondary orbital interactions, has been proposed for the closely related reaction of enamines with α,β-unsaturated systems.[38]

Conclusions

In summary, an efficient protocol for the nucleophilic formylation of conjugated enones has been developed, based on the use of bulky trialkylsilyl triflates as promoters. This strategy simultaneously provides the necessary activation of the conjugated enone and conditions for trapping the enolates actually generated during the Michael reaction. In addition, the reaction specifically gives rise to 1,4-adducts, and the stereoselectivity for the addition of SAMP-derived formaldehyde hydrazones is shown to be excellent. The overall formylation and cyanation protocols take advantage of the efficiency and mildness of the dialkylhydrazone cleavage reactions to afford both aldehydes and nitriles.

In terms of the obtained products, the process described in this paper offers a new route to racemic and optically enriched 4-oxo aldehydes and 4-oxo nitriles, some of them bearing new stereogenic quaternary centers. Many other synthetic possibilities may be envisaged for the intermediates **3**−**6**. For instance, the same azomethinic carbon atom of hydrazones that served as nucleophile may now, exhibiting its versatility, be used as an electrophile and suffer addition of organometallic compounds.[39]

From a more general point of view, a comparison between FDAHs as formyl anion equivalents and other available methodologies should consider many different aspects. In our opinion, the following points are remarkable advantages of the FDAH methodology:

(i) The reagents can be easily and economically generated; they can be stored and handled without particular care. FDAHs are actually formyl anion equivalents; no strong bases are needed.

(ii) The range of electrophilic substrates (nitroalkenes, carbonyl compounds, conjugated enones) efficiently formylated up to now opens access to a wide variety of compounds.

(iii) The regeneration of the carbonyl function is an easy and clean operation. Alternatively, dialkylhydrazones can be considered as precursors of nitriles.

(iv) A chiral version of the reaction, which allows access to both enantiomers of each synthesized compound, has also been developed.

The extension of this methodology to dialkylhydrazones different to those derived from formaldehyde (i.e., the development of a more general nucleophilic acylation protocol) as well as the reactivity toward other electrophilic substrates, is currently under study in our laboratory.

Experimental Section

General Experimental Data. Melting points were determined using a metal block and are uncorrected. Optical rotations were measured at room temperature. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ with either TMS (0.00 ppm ^1H, 0.00 ppm ^{13}C) or $CDCl_3$ (7.26 ppm ^1H, 77.00 ppm ^{13}C) as an internal reference. Quantitative ^1H NMR measurements were carried out at 298 K at 500 and 300 MHz in 5-mm NMR tubes using a 90° pulse angle and a pulse delay of 1.5 s. Quantitative ^{13}C NMR measurements were carried out at 298 K at 125 and 75 MHz in 5-mm NMR tubes. The spectra were completely proton decoupled; a 90° pulse angle and a pulse delay of 2 s were used. The data were processed three times, and the average value is reported. The sensitivity of the method was examined by adding increasing amounts of **8i** to a sample solution containing known amounts of **8h**. This assay was able to detect **8i** at a concentration equal to 0.5 mol % of the major component **8h**. FT-IR spectra were recorded for KBr pellets or films. EI-mass spectra were obtained at 70 eV, using an ionizing current of 100 μA, an accelerating voltage of 4 kV, and a resolution of 1000 or 10 000 (10% valley definition). The reactions were monitored by TLC. Purification of the products was carried out by flash chromatography (silica gel, 0.063−0.200 nm). The light petroleum ether (PE) used had boiling range 40−65 °C. Tetrahydrofuran (THF) was distilled from sodium−benzophenone ketyl immediately prior to use. Elemental analyses were carried out at the Instituto Químico de Sarriá (Barcelona, Spain) and the Departamento de Química Analítica, Universidad de Sevilla (Seville, Spain). Formaldehyde dimethylhydrazone (**1a**)[17a] and (−)-(*S*)-2-(methoxymethyl)-1-(methyleneamino)pyrrolidine (**1b**)[19d] were prepared according to the literature. Enones **2**, TBDMSOTf, and TDSOTf were obtained from commercial suppliers.

Synthesis of Silyl Enol Ethers 3. Method A. To a cooled (0 °C) solution of enone **2** (2 mmol) in dry ether (10 mL) were added dropwise trialkylsilyl (TBDMS or TDS) triflate (2.5 mmol) followed by a solution of **1a** (0.34 mL, 4 mmol) in dry ether (4 mL) over 10 min under an argon atmosphere. The mixture was stirred for 15 min, quenched with saturated $NaHCO_3$ solution, and purified by column chromatography.

Method B. To a cooled (0 °C) solution of enone **2** (1 mmol) in dry ether (5 mL) were added **1a** (0.17 mL, 2 mmol) and then dropwise TDSOTf (0.32 mL, 1.25 mmol) under an argon atmosphere. The mixture was stirred at 0 °C until TLC indicated no further change and then quenched with saturated $NaHCO_3$ and the product purified by column chromatography.

Methods followed for synthesis, chromatography solvents, yields, and spectral and analytical data for compounds **3** are as follows:

3-[(Dimethylthexylsilyl)oxy]-2-cyclopentene-1-carboxaldehyde Dimethylhydrazone (3a). Following method A from **2a** and TDSOTf, flash chromatography (1:6 Et_2O−PE) gave **3a** as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.20 (s, 6H),

(37) Agami, C.; Fadlallah, M.; Levisalles, J. *Tetrahedron* **1981**, *37*, 903.

(38) Pfau, M.; Tomas, A.; Lim, S.; Revial, G. *J. Org. Chem.* **1995**, *60*, 1143. See also: Cavé, C.; Desmaële, D.; d'Angelo, J.; Riche, C.; Chiaroni, A. *J. Org. Chem.* **1996**, *61*, 4361 and references cited therein.

(39) Martín-Zamora, E.; Díez, E.; Fernández, R.; Lassaletta, J. M. Unpublished results.

0.87−0.91 (m, 12H), 1.65 (m, 1H, J = 6.7 Hz), 1.72 (dddd, 1H, J = 13.5, 8.9, 7.3, 5.7 Hz), 2.15 (dtd, 1H, J = 13.5, 8.1, 6.1 Hz), 2.28−2.32 (m, 2H), 2.72 (s, 6H), 3.42−3.47 (m, 1H), 4.55 (br s, 1H), 6.48 (d, 1H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ −2.9, −2.8, 18.3, 20.0, 24.8, 26.8, 33.2, 33.9, 43.2, 45.4, 103.8, 143.4, 156.6; IR (film, cm^{-1}) 2868, 1642, 1466; mass spectrum m/z (rel intensity) 296 M$^+$ (5), 224 (26), 73 (100); m/z calcd for $C_{16}H_{32}N_2OSi$ 296.2284, found 296.2285.

3-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclopentene-1-carboxaldehyde Dimethylhydrazone (3a′). Following method A from **2a** and TBDMSOTf, flash chromatography (1:6 Et_2O−PE) gave **3a′** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 6H), 0.91 (s, 9H), 1.70 (dddd, 1H, J = 13.1, 8.9, 7.4, 5.7 Hz), 2.16 (dtd, 1H, J = 13.1, 8.2, 6.2 Hz), 2.27−2.30 (m, 2H), 2.70 (s, 6H), 3.40−3.45 (m, 1H), 4.55 (m, 1H, J = 1.9 Hz), 6.46 (d, 1H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.8, 17.9, 25.5, 26.8, 33.1, 43.1, 45.4, 103.8, 143.1, 156.7; IR (film, cm^{-1}) 2853, 1643, 1468; mass spectrum m/z (rel intensity) 268 M$^+$ (10), 223 (61), 196 (54), 73 (100); m/z calcd for $C_{14}H_{28}N_2OSi$ 268.1971, found 268.1963.

3-[(Dimethylthexylsilyl)oxy]-2-cyclohexene-1-carboxaldehyde Dimethylhydrazone (3d). Following method A from **2d** and TDSOTf, flash chromatography (1:6 Et_2O−PE) gave **3d** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.15 (s, 3H), 0.88 (s, 6H), 0.90 (d, 3H, J = 7.0 Hz), 0.91 (d, 3H, J = 7.0 Hz), 1.37−1.45 (m, 1H), 1.58−1.71 (m, 2H), 1.65 (m, 1H, J = 7.0 Hz), 1.75−1.82 (m, 1H), 1.97−2.07 (m, 2H), 2.73 (s, 6H), 3.02−3.07 (m, 1H), 4.78−4.80 (m, 1H), 6.47 (d, 1H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −1.5, 18.5, 20.1, 21.2, 24.8, 27.7, 29.7, 34.1, 38.8, 43.3, 105.6, 142.8, 151.8; IR (film, cm^{-1}) 2866, 1663; mass spectrum m/z (rel intensity) 310 M$^+$ (13), 265 (34), 238 (52) 73 (100); m/z calcd for $C_{17}H_{34}N_2OSi$ 310.2440, found 310.2444.

3-[(*tert*-Butyldimethylsilyl)oxy]-2-cyclohexene-1-carboxaldehyde Dimethylhydrazone (3d′). Following method A from **2d** and TBDMSOTf, flash chromatography (1:6 Et_2O−PE) gave **3d′** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 6H), 0.93 (s, 9H), 1.61−1.66 (m, 1H), 1.76−1.81 (m, 3H), 2.01−2.18 (m, 2H), 2.72 (s, 6H), 3.03−3.10 (m, 1H), 4.80 (br s, 1H), 6.45 (d, 1H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −3.7, 17.9, 20.3, 25.6, 27.5, 29.2, 38.7, 43.2, 105.5, 142.7, 151.8; IR (film, cm^{-1}) 2855, 1688; mass spectrum m/z (rel intensity) 282 M$^+$ (20), 237 (56), 210 (89) 73 (100); m/z calcd for $C_{15}H_{30}N_2OSi$ 282.2127, found 282.2133.

6,6-Dimethyl-3-[(dimethylthexylsilyl)oxy]-2-cyclohexene-1-carboxaldehyde Dimethylhydrazone (3f). Following method A from **2f** and TDSOTf, flash chromatography (1:10 Et_2O−PE) gave 405 mg (60%) of **3f** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.85 (s, 3H), 0.87 (s, 6H), 0.89 (d, 6H, J = 6.9 Hz), 0.96 (s, 3H), 1.41 (dt, 1H, J = 13.2, 6.6 Hz), 1.51 (dt, 1H, J = 13.2, 6.6 Hz), 1.66 (m, 1H, J = 6.9 Hz), 2.00−2.04 (m, 2H), 2.67 (ddt, 1H, J = 7.9, 3.9, 1.9 Hz), 2.72 (s, 6H), 4.68 (dd, 1H, J = 3.9, 1.3 Hz), 6.44 (d, 1H, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.6, −2.5, 18.4, 20.0, 24.4, 24.8, 27.4, 27.6, 31.3, 34.0, 34.9, 43.4, 48.7, 104.9, 141.1, 150.5; IR (film, cm^{-1}) 2888, 1663, 1485; mass spectrum m/z (rel intensity) 338 M$^+$ (19), 293 (50), 266 (17); m/z calcd for $C_{19}H_{38}N_2OSi$ 338.2753, found 338.2753.

***cis*-6-*tert*-Butyl-3-[(dimethylthexylsilyl)oxy]-2-cyclohexene-1-carboxaldehyde Dimethylhydrazone (3g).** Following method B from **2g**, flash chromatography (1:8 Et_2O−PE) afforded unreacted **2g** (33%) and 190 mg (52%) of **3g** as an oil: bp 120−125 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.85 (s, 6H), 0.90 (d, 6H, J = 6.9 Hz), 0.91 (s, 9H), 1.28 (ddd, 1H, J = 10.9, 8.0, 3.8 Hz), 1.42 (dtd, 1H, J = 12.9, 10.9, 5.1 Hz), 1.64 (m, 1H, J = 6.9 Hz), 1.79 (ddt, 1H, J = 12.9, 4.8, 3.8 Hz), 1.93 (dtd, 1H, J = 17.0, 5.1, 1.4 Hz), 2.03 (dddd, 1H, J = 17.0, 10.2, 4.8, 2.5 Hz), 2.66 (s, 6H), 3.05−3.07 (m, 1H), 4.50−4.51 (m, 1H), 6.41 (d, 1H, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.7, −2.6, 18.3, 19.9, 23.9, 24.6, 28.9, 30.0, 33.7, 33.8, 41.0, 43.3, 46.7, 106.2, 146.7, 151.6; IR (film, cm^{-1}) 2868, 1669, 1466; mass spectrum m/z (rel intensity) 366 M$^+$ (26), 321 (24) 73 (100); m/z calcd for $C_{21}H_{42}N_2OSi$ 366.3066, found 366.3077.

4-[(Dimethylthexylsilyl)oxy]-2,4-diphenyl-3-butenal Dimethylhydrazone (3h). Following method B from **2h**, flash chromatography [1:100 → 1:50 ethyl acetate−petroleum ether (EA−PE)] gave 211 mg (50%) of **3h** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ −0.17 (s, 3H), 0.01 (s, 3H), 0.92−0.94 (m, 12H), 1.74 (m, 1H, J = 6.8 Hz), 2.75 (s, 6H), 4.82 (dd, 1H, J = 9.9, 6.1 Hz), 5.39 (dd, 1H, J = 9.9, 0.8 Hz), 6.67 (d, 1H, J = 6.1 Hz), 7.16−7.48 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, −1.9, 18.5, 18.6, 20.2, 20.3, 25.1, 33.8, 43.2, 44.8, 111.3, 126.0, 126.4, 127.6, 127.7, 127.8, 128.3, 138.8, 139.8, 142.9, 149.9; IR (film, cm^{-1}) 2868, 1601, 1489; mass spectrum m/z (rel intensity) 422 M$^+$ (9), 378 (7) 75 (100); m/z calcd for $C_{26}H_{38}N_2OSi$ 422.2753, found 422.2757.

4-[(*tert*-Butyldimethylsilyl)oxy]-2,4-diphenyl-3-butenal Dimethylhydrazone (3h′). Following method B from **2h**, flash chromatography (1:100 → 1:50 EA−PE) gave 229 mg (58%) of **3h′** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.15 (s, 3H), 1.13 (s, 9H), 2.90 (s, 6H), 4.98 (dd, 1H, J = 9.9, 6.1 Hz), 5.58 (d, 1H, J = 9.9 Hz), 6.83 (d, 1H, J = 6.1 Hz), 7.31−7.66 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.0, 18.2, 25.8, 43.1, 44.8, 111.0, 126.0, 126.3, 127.6, 127.7, 128.3, 138.8, 139.8, 142.9, 149.9; IR (film, cm^{-1}) 2857, 1652, 1599, 1489; mass spectrum m/z (rel intensity) 394 M$^+$ (37), 350 (38), 323 (33) 73 (100); m/z calcd for $C_{24}H_{34}N_2OSi$ 394.2440, found 394.2449.

Synthesis of 4-Oxo Hydrazones 4. Method A. This method was described above for the synthesis of **3** (method A, using TDSOTf). After stirring, TBAF (1M in THF, 2.5 mL) was added and the mixture diluted with Et_2O (20 mL) and washed with brine. The combined organic layer was concentrated, and the residue was purified by column chromatography.

Method B. This method was described above for the synthesis of **3** (method B). After stirring, TBAF (1 M in THF, 2.5 mL) was added and the mixture diluted with Et_2O (20 mL) and washed with brine. The combined organic layer was concentrated, and the residue was purified by column chromatography.

The methods followed for synthesis, chromatography solvents, yields, and spectral and analytical data for compounds **4** are as follows.

3-Oxocyclopentane-1-carboxaldehyde Dimethylhydrazone (4a). Following method A from **2a**, flash chromatography (1:1 → 2:1 Et_2O−PE) gave 222 mg (72%) of **4a** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.90 (dtd, 1H, J = 13.6, 8.7, 3.5 Hz), 2.16−2.24 (m, 1H), 2.23- 2.25 (m, 1H), 2.29 (dd, 1H, J = 18.4, 8.2 Hz), 2.35 (td, 1H, J = 13.9, 8.3 Hz), 2.43 (dd, 1H, J = 18.4, 7.8 Hz), 2.76 (s, 6H), 3.03−3.11 (m, 1H), 6.58 (d, 1H, J = 5.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.1, 37.7, 39.7, 42.8, 42.9, 137.6, 218.5; IR (film, cm^{-1}) 2863, 1740, 1649; mass spectrum m/z (rel intensity) 154 M$^+$ (100), 83 (49); m/z calcd for $C_8H_{14}N_2O$ 154.1106, found 154.1111.

1-Methyl-3-oxocyclopentane-1-carboxaldehyde Dimethylhydrazone (4b). Following method A from **2b**, flash chromatography (1:1 Et_2O−PE) gave 306 mg (91%) of **4b** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 3H), 1.78 (dt, 1H, J = 12.4, 8.5 Hz), 2.00 (d, 1H, J = 1.78 Hz), 2.12 (dddd, 1H, J = 12.7, 8.7, 5.2, 1.5 Hz), 2.22 (dddd, 1H, J = 18.7, 8.4, 5.2, 1.1 Hz), 2.29 (dtd, 1H, J = 18.7, 8.6, 1.0 Hz), 2.61 (d, 1H, J = 17.8 Hz), 2.69 (s, 6H), 6.50 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.5, 29.7, 34.6, 36.9, 43.8, 49.9, 141.3, 210.4; mass spectrum m/z (rel intensity) 168 M$^+$ (28), 57 (100); m/z calcd for $C_9H_{16}N_2O$ 168.1263, found 168.1254.

3-Oxocyclohexane-1-carboxaldehyde Dimethylhydrazone (4d). Following method A from **2d**, flash chromatography (1:1 → 2:1 Et_2O−PE) gave 102 mg (75%) of **4d** as an oil: bp 206 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.62 (ddt, 1H, J = 12.4, 10.0, 3.1 Hz), 1.72 (dddt, 1H, J = 13.5, 11.6, 4.9, 3.2 Hz), 1.97−2.03 (m, 1H), 2.04−2.10 (m, 1H), 2.29 (dddd, 1H, J = 14.4, 11.6, 6.0, 1.1 Hz), 2.35−2.40 (m, 1H), 2.37 (ddd, 1H, J = 14.3, 11.1, 1.1 Hz), 2.50 (ddt, 1H, J = 14.3, 4.2, 1.8 Hz), 2.66−2.73 (m, 1H), 2.74 (s, 6H), 6.51 (d, 1H, J = 5.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.5, 29.7, 41.1, 42.9, 45.4, 67.8, 138.2, 218.7; IR (film, cm^{-1}) 2863, 1711; mass spectrum m/z (rel intensity) 168 M$^+$ (100). Anal. Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.58; N, 16.65. Found: C, 63.79; H, 9.40; N, 17.02.

2,2-Dimethyl-5-oxocyclohexanecarboxaldehyde Dimethylhydrazone (4f). Following method A from **2f**, flash

chromatography (1:4 → 1:3 Et_2O−PE) gave unreacted **2f** (4%) and 224 mg (65%) of **4f** as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.08 (s, 3H), 1.64 (td, 1H, J = 12.5, 5.0 Hz), 1.74 (ddd, 1H, J = 13.0, 5.8, 5.0 Hz), 2.31 (dtd, 1H, J = 15.3, 5.0, 1.9 Hz), 2.35−2.50 (m, 4H), 2.73 (s, 6H), 6.52 (d, 1H, J = 5.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 28.6, 32.8, 37.8, 39.1, 41.6, 43.0, 49.4, 136.5, 211.1; IR (film, cm^{-1}) 2824, 1712; mass spectrum m/z (rel intensity) 196 M^+ (100), 152 (38), 125 (13); m/z calcd for $C_{11}H_{20}N_2O$ 196.1576, found 196.1578.

***cis*-2-*tert*-Butyl-5-oxocyclohexane-1-carboxaldehyde Dimethylhydrazone (4g).** Following method B from **2g**, flash chromatography (1:2 Et_2O−PE) gave unreacted **2g** (33%) and 123 mg (55%) of **4g** as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.54 (dtd, 1H, J = 15.5, 13.5, 3.6 Hz), 1.67 (dt,-1H, J = 12.0, 5.1 Hz), 1.91 (dtd, 1H, J = 5.1, 4.8, 3.6 Hz), 2.14 (ddd, 1H, J = 17.5, 15.5, 4.8 Hz), 2.28 (dt, 1H, J = 17.5, 3.6 Hz), 2.35 (dd, 1H, J = 15.6, 6.1 Hz), 2.40 (dd, 1H, J = 15.6, 4.9 Hz), 2.62 (s, 6H), 2.75 (m, 1H), 6.45 (d, 1H, J = 5.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.9, 27.5, 33.9, 37.9, 38.6, 42.3, 42.9, 46.7, 141.2, 212.4; IR (film, cm^{-1}) 2868, 1717, 1468; mass spectrum m/z (rel intensity) 224 M^+ (100). Anal. Calcd for $C_{13}H_{24}N_2O$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.32; H, 10.78; N, 12.64.

4-Oxo-2,4-diphenylbutanal Dimethylhydrazone (4h). Following method B from **2h**, flash chromatography (1:9 Et_2O−PE) gave 190 mg (68%) of crystalline **4h**: mp 86−88 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.63 (s, 6H), 3.04 (dd, 1H, J = 16.5, 5.6 Hz), 3.91 (dd, 1H, J = 16.5, 8.5 Hz), 4.37 (ddd, 1H, J = 8.9, 5.7, 3.7 Hz), 6.73 (d, 1H, J = 3.7 Hz), 7.21−7.98 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.5, 44.3, 126.7, 128.1, 128.2, 128.3, 128.6, 132.5, 137.1, 137.6, 142.4, 198.9; IR (KBr, cm^{-1}) 1678, 1595; mass spectrum m/z (rel intensity) 280 M^+ (20), 236 (100). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 77.19; H, 7.18; N, 9.90.

2-Phenyl-4-oxopentanal Dimethylhydrazone (4i). Following method A from **2i**, flash chromatography (1:3 Et_2O−PE) gave 240 mg (55%) of **4i** as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.59 (dd, 1H, J = 16.3, 5.5 Hz), 2.74 (s, 6H), 3.28 (dd, 1H, J = 16.3, 9.0 Hz), 4.15 (ddd, 1H, J = 9.0, 5.4, 3.8 Hz), 6.67 (d, 1H, J = 3.7 Hz), 7.23−7.37 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.6, 42.9, 44.0, 47.1, 126.6, 127.9, 128.5, 137.2, 141.9, 207.5; IR (KBr, cm^{-1}) 2850, 1707, 1558; mass spectrum m/z (rel intensity) 218 M^+ (28), 200 (100). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.18; H, 8.15; N, 13.04.

Synthesis of Silyl Enol Ethers 5. To a cooled (−78 °C) solution of enone **2** (5 mmol) in dry THF (5 mL) were sequentially added TDSOTf (1.41 mL, 5.5 mmol) and precooled (−78 °C) **1b** (0.89 mL, 6.25 mmol) under an argon atmosphere. After 15 min, $NaHCO_3$ (s, 0.5 g) was added, and the mixture was allowed to warm to rt, diluted with Et_2O (50 mL), and washed with H_2O (2 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (Et_2O−PE) to yield pure compounds **5**. Compound **5i** was detected, but it decomposed and could not be characterized. Chromatography solvents, yields, and spectral and analytical data for compounds **5** are as follows.

(2*S*)-1-[[(1*R*)-[3-[(Dimethylthexylsilyl)oxy]-2-cyclopentenyl]methylene]amino]-2-(methoxymethyl)pyrrolidine (5a). From **2a**, flash chromatography (1:6 Et_2O−PE) gave 1.17 g (64%) of **5a** as an oil: $[\alpha]^{22}_D$ −13.2° (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 3H), 0.21 (s, 3H), 0.87−0.92 (m, 12H), 1.62−1.96 (m, 6H), 2.13−2.17 (m, 1H), 2.27−2.31 (m, 2H), 2.68−2.73 (m, 1H), 3.35−3.43 (m, 3H), 3.39 (s, 3H), 3.43 (dd, 1H, J = 9.1, 6.9 Hz), 3.58 (dd, 1H, J = 9.1, 3.8 Hz), 4.56−4.58 (m, 1H), 6.49 (d, 1H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.7, −2.6, 18.5, 20.1, 22.1, 25.0, 26.6, 27.2, 33.3, 34.1, 45.7, 50.5, 59.2, 63.5, 74.9, 104.1, 143.4, 156.5; IR (film, cm^{-1}) 2872, 1641; mass spectrum m/z (rel intensity) 366 M^+ (12), 321 (53), 73 (100). Anal. Calcd for $C_{20}H_{38}N_2O_2Si$: C, 65.52; H, 10.45; N, 7.64. Found: C, 65.31; H, 10.80; N, 7.33.

(2*S*)-1-[[(1*R*)-[3-[(Dimethylthexylsilyl)oxy]-1-methyl-2-cyclopentenyl]methylene]amino]-2-(methoxymethyl)-pyrrolidine (5b). From **2b**, flash chromatography (1:15 Et_2O−PE) gave 1.45 g (76%) of **5b** as an oil: $[\alpha]^{22}_D$ −36.1° (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 3H), 0.19 (s, 3H), 0.87−0.90 (m, 12H), 1.18 (s, 3H), 1.62−1.68 (m, 2H), 1.75−1.97 (m, 4H), 2.04 (ddd, 1H, J = 12.7, 8.6, 6.3 Hz), 2.25−2.37 (m, 2H), 2.63−2.70 (m, 1H), 3.26−3.36 (m, 2H), 3.38 (s, 3H), 3.44 (dd, 1H, J = 9.2, 7.0 Hz), 3.61 (dd, 1H, J = 9.2, 3.6 Hz), 4.53 (t, 1H, J = 1.6 Hz), 6.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.8, 18.4, 20.0, 21.8, 24.9, 25.4, 26.4, 32.9, 34.0, 34.5, 48.2, 49.9, 59.0, 63.4, 74.6, 110.5, 145.5, 154.4; IR (film, cm^{-1}) 2870, 1643; mass spectrum m/z (rel intensity) 380 M^+ (26), 335 (100); m/z calcd for $C_{21}H_{40}N_2O_2Si$ 380.2859, found 380.2857.

(2*S*)-1-[[(1*R*)-[3-[(Dimethylthexylsilyl)oxy]-2-methyl-2-cyclopentenyl]methylene]amino]-2-(methoxymethyl)-pyrrolidine (5c). From **2c**, flash chromatography (1:5 Et_2O−PE) gave 1.46 g (77%) of **5c** as an oil: $[\alpha]^{22}_D$ +23.1° (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 3H), 0.16 (s, 3H), 0.87−0.92 (m, 12H), 1.50 (td, 3H, J = 2.0, 1.1 Hz), 1.64−1.71 (m, 1H), 1.68 (m, 1H, J = 6.8 Hz), 1.78−1.96 (m, 4H), 2.11 (dtd, 1H, J = 14.0, 9.0, 5.2 Hz), 2.26−2.33 (m, 2H), 2.72−2.77 (m, 1H), 3.17−3.23 (m, 1H), 3.30−3.34 (m, 1H), 3.37 (s, 3H), 3.38−3.41 (m, 1H), 3.43 (dd, 1H, J = 8.8, 6.8 Hz), 3.57 (dd, 1H, J = 8.8, 3.3 Hz), 6.45 (d, 1H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.0, 10.6, 18.5, 20.0, 22.0, 24.9, 26.0, 26.5, 32.7, 33.9, 48.8, 50.4, 59.1, 63.4, 74.6, 113.7, 142.8, 148.2; IR (film, cm^{-1}) 2875, 1685, 1466; mass spectrum m/z (rel intensity) 380 M^+ (16), 335 (41), 265 (100); m/z calcd for $C_{21}H_{40}N_2O_2Si$ 380.2859, found 380.2859.

(2*S*)-1-[[(1*R*)-[3-[(Dimethylthexylsilyl)oxy]-1-methyl-2-cyclohexenyl]methylene]amino]-2-(methoxymethyl)pyrrolidine (5e). From **2e**, flash chromatography (1:10 Et_2O−PE) gave 1.62 g (82%) of **5e** as an oil: $[\alpha]^{22}_D$ −36.8° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.86−0.90 (m, 12H), 1.10 (s, 3H), 1.24−2.00 (m, 11H), 2.60−2.69 (m, 1H), 3.24−3.34 (m, 2H), 3.36 (s, 3H), 3.43 (dd, 1H, J = 9.2, 6.9 Hz), 3.59 (dd, 1H, J = 9.2, 3.6 Hz), 4.70 (s, 1H), 6.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.6, −2.5, 18.4, 19.4, 20.0, 21.8, 24.7, 26.3, 26.9, 29.7, 33.9, 34.3, 38.6, 49.8, 59.0, 63.4, 74.5, 111.8, 145.6, 150.1; IR (film, cm^{-1}) 1657, 1458; mass spectrum m/z (rel intensity) 394 M^+ (8), 349 (100). Anal. Calcd for $C_{22}H_{42}N_2O_2Si$: C, 66.95; H, 10.73; N, 7.10. Found: C, 66.89; H, 11.05; N, 7.00.

(2*S*)-1-[[(1*R*)-[6,6-Dimethyl-3-[(dimethylthexylsilyl)-oxy]-2-cyclohexenyl]methylene]amino]-2-(methoxymethyl)pyrrolidine (5f). From **2f**, flash chromatography (1:15 → 1:10 Et_2O−PE) gave 1.51 g (74%) of **5f** as an oil: $[\alpha]^{22}_D$ +11.6° (*c* 1, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 0.17 (s, 6H), 0.85−0.96 (m, 18H), 1.40−2.06 (m, 9H), 2.65−2.67 (m, 1H), 2.67−2.71 (m, 1H), 3.37−3.40 (m, 2H), 3.38 (s, 3H), 3.43 (dd, 1H, J = 9.1, 6.9 Hz), 3.57 (dd, 1H, J = 9.0, 3.8 Hz), 4.72 (d, 1H, J = 3.6 Hz), 6.47 (d, 1H, J = 7.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −2.5, 18.4, 20.0, 22.0, 23.9, 24.7, 26.4, 27.4, 27.7, 31.3, 33.9, 35.3, 48.6, 50.8, 59.1, 63.5, 74.8, 104.9, 140.8, 150.2; IR (film, cm^{-1}) 2868, 1665, 1464; mass spectrum m/z (rel intensity) 408 M^+ (22), 363 (56), 73 (100). Anal. Calcd for $C_{23}H_{44}N_2O_2Si$: C, 67.59; H, 10.85; N, 6.85. Found: C, 67.66; H, 10.90; N, 6.66.

(2*S*)-1-[[(1*R*)-4-[(Dimethylthexylsilyl)oxy]-2,4-diphenyl-3-butenylidene]amino]-2-(methoxymethyl)pyrrolidine (5h). From **2h**, flash chromatography (1:10 Et_2O−PE) gave 1.85 g (75%) of **5h** as an oil: $[\alpha]^{22}_D$ −49.6° (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.17 (s, 3H), 0.28 (s, 3H), 1.01−1.11 (m, 13H), 1.75−2.14 (m, 4H), 2.88−2.93 (m, 1H), 3.43−3.47 (m, 2H), 3.53 (s, 3H), 3.62−3.65 (m, 1H), 3.80 (dd, 1H, J = 8.9, 3.2 Hz), 4.96 (dd, 1H, J = 10.0, 5.9 Hz), 5.54 (d, 1H, J = 10.0 Hz), 6.82 (d, 1H, J = 5.9 Hz), 7.30−7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −2.0, −1.9, 18.5, 18.6, 20.2, 20.3, 21.8, 25.1, 26.4, 33.8, 44.9, 49.6, 59.1, 63.3, 74.5, 111.6, 126.0, 126.3, 127.5, 127.7, 127.8, 128.8, 138.5, 139.8, 143.0, 149.7; IR (film, cm^{-1}) 2870, 1645, 1599; mass spectrum m/z (rel intensity) 492 M^+ (49), 447 (57), 73 (100). Anal. Calcd for $C_{30}H_{44}N_2O_2Si$: C, 73.12; H, 9.00; N, 5.68. Found: C, 73.24; H, 8.80; N, 5.45.

Synthesis of 4-Oxo Hydrazones 6. To a cooled (−78 °C) solution of enone **2** (5 mmol) in dry THF (5 mL) were sequentially added TDSOTf (1.41 mL, 5.5 mmol) and precooled (−78 °C) **1b** (0.89 mL, 6.25 mmol) under an argon atmosphere.

After 15 min, TBAF (1 M in THF, 5.5 mL, 5.5 mmol) was added, and the mixture was allowed to warm to rt and stirred until TLC indicated total consumption of the silyl enol ether **5**. The mixture was then diluted with Et_2O (50 mL) and washed with H_2O (2 × 30 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography. Eluants, yields, and spectral and analytical data for compounds **6** are as follows.

(2*S*)-2-(Methoxymethyl)-1-[[(1*R*)-(3-oxocyclopentyl)-methylene]amino]pyrrolidine (6a). From **2a**, flash chromatography (1:4 → 1:1 Et_2O−PE) gave 0.72 g (69%) of **6a** as an oil: $[\alpha]^{22}_D$ −112.5° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75−2.00 (m, 5H), 2.14−2.34 (m, 4H), 2.39 (dd, 1H, *J* = 18.4, 7.8 Hz), 2.72−2.77 (m, 1H), 3.04−3.08 (m, 1H), 3.33−3.41 (m, 2H), 3.37 (s, 3H), 3.44 (dd, 1H, *J* = 9.2, 6.4 Hz), 3.54 (dd, 1H, *J* = 9.2, 3.8 Hz), 6.59 (d, 1H, *J* = 5.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 26.4, 28.1, 37.4, 39.6, 42.7, 49.7, 59.1, 63.2, 74.4, 137.4, 218.7; IR (film, cm^{-1}) 2880, 1742; mass spectrum *m*/*z* (rel intensity) 224 M^+ (5), 179 (100); *m*/*z* calcd for $C_{12}H_{20}N_2O_2$ 224.1525, found 224.1524.

(2*S*)-2-(Methoxymethyl)-1-[[(1*R*)-(1-methyl-3-oxocyclopentyl)methylene]amino]pyrrolidine (6b). From **2b**, flash chromatography (1:2 Et_2O−PE) gave 0.95 g (80%) of **6b** as an oil: $[\alpha]^{22}_D$ −210.4° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.79−1.98 (m, 5H), 1.99 (d, 1H, *J* = 17.6 Hz), 2.12 (dddd, 1H, *J* = 13.0, 8.7, 4.4, 1.8 Hz), 2.22 (ddd, 1H, *J* = 18.8, 8.4, 4.4 Hz), 2.24−2.34 (m, 1H), 2.63 (d, 1H, *J* = 17.6 Hz), 2.67−2.72 (m, 1H), 3.27−3.33 (m, 2H), 3.36 (s, 3H), 3.45 (dd, 1H, *J* = 9.4, 6.1 Hz), 3.52 (dd, 1H, *J* = 9.4, 3.6 Hz), 6.52 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 25.4, 26.1, 34.6, 36.7, 42.8, 49.3, 49.6, 58.9, 63.2, 74.0, 141.0, 219.0; IR (film, cm^{-1}) 2876, 1742; mass spectrum *m*/*z* (rel intensity) 238 M^+ (8), 193 (100). Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75. Found: C, 65.49; H, 9.56; N, 11.42.

(2*S*)-2-(Methoxymethyl)-1-[[(1*R*,2*R*)-(2-methyl-3-oxocyclopentyl)methylene]amino]pyrrolidine (6c). From **2c**, flash chromatography (1:3 Et_2O−PE) gave 0.98 g (82%) of **6c** as an oil: $[\alpha]^{22}_D$ −69.9° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (d, 3H, *J* = 7.0 Hz), 1.72−1.82 (m, 2H), 1.88−1.99 (m, 3H), 2.08−2.11 (m, 1H), 2.13−2.20 (m, 2H), 2.40 (ddd, 1H, *J* = 17.3, 8.5, 1.4 Hz), 2.47−2.52 (m, 1H), 2.75−2.80 (m, 1H), 3.32−3.36 (m, 1H), 3.37 (s, 3H), 3.40−3.42 (m, 1H), 3.45 (dd, 1H, *J* = 8.6, 6.5 Hz), 3.55 (dd, 1H, *J* = 8.6, 3.1 Hz), 6.56 (d, 1H, *J* = 5.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.4, 22.0, 26.2, 26.4, 36.9, 48.0, 48.6, 49.8, 59.1, 63.2, 74.4, 137.6, 219.9; IR (film, cm^{-1}) 2875, 1740; mass spectrum *m*/*z* (rel intensity) 238 M^+ (4), 193 (100). Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.30; N, 11.75. Found: C, 65.71; H, 9.58; N, 12.02.

(2*S*)-2-(Methoxymethyl)-1-[[(1*R*)-(1-methyl-3-oxocyclohexyl)methylene]amino]pyrrolidine (6e). From **2e**, flash chromatography (1:4 Et_2O−PE) gave 1.09 g (86%) of **6e** as an oil: $[\alpha]^{22}_D$ −164.5° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.59−1.66 (m, 1H), 1.75−2.00 (m, 7H), 2.09 (dd, 1H, *J* = 14.3, 1.2 Hz), 2.19 (dt, 1H, *J* = 13.6, 7.7 Hz), 2.31 (dtt, 1H, *J* = 13.2, 6.7, 1.35 Hz), 2.58 (dt, 1H, *J* = 14.3, 1.5 Hz), 2.65−2.71 (m, 1H), 3.25−3.32 (m, 2H), 3.37 (s, 3H), 3.47 (dd, 1H, *J* = 9.5, 5.9 Hz), 3.52 (dd, 1H, *J* = 9.5, 3.5 Hz), 6.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.7, 25.7, 26.6, 35.3, 40.4, 41.8, 49.2, 51.1, 59.1, 63.2, 73.9, 141.6, 210.7; IR (film, cm^{-1}) 2876, 1711; mass spectrum *m*/*z* (rel intensity) 252 M^+ (4), 207 (100). Anal. Calcd for $C_{14}H_{24}N_2O_2$: C, 66.66; H, 9.58; N, 11.10. Found: C, 66.65; H, 9.84; N, 11.36.

(2*S*)-1-[[(1*R*)-(2,2-Dimethyl-5-oxocyclohexyl)methylene]-amino]-2-(methoxymethyl)pyrrolidine (6f). From **2f**, flash chromatography (1:4 → 1:1 Et_2O−PE) gave 1.05 g (79%) of **6f** as an oil: $[\alpha]^{22}_D$ −76.3° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.08 (s, 3H), 1.61 (ddd, 1H, *J* = 13.6, 11.5, 5.3 Hz), 1.74 (ddd, 1H, *J* = 13.6, 6.0, 4.9 Hz), 1.77−1.98 (m, 4H), 2.29 (dtd, 1H, *J* = 15.3, 5.1, 1.9 Hz), 2.37−2.52 (m, 4H), 2.70−2.75 (m, 1H), 3.31−3.38 (m, 2H), 3.36 (s, 3H), 3.44 (dd, 1H, *J* = 9.3, 6.3 Hz), 3.52 (dd, 1H, *J* = 9.3, 3.8 Hz), 6.55 (d, 1H, *J* = 5.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 21.9, 26.3, 28.5, 32.9, 37.8, 38.9, 41.7, 49.5, 49.9, 59.1, 63.3, 74.3, 136.4, 211.2; IR (film, cm^{-1}) 1713, 1597; mass spectrum *m*/*z* (rel intensity) 266 M^+ (4), 221 (100). Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.39; H, 9.99; N, 10.40.

(2*S*)-1-[[(1*R*)-4-Oxo-2,4-diphenylbutylidene]amino]-2-(methoxymethyl)pyrrolidine (6h). From **2h**, flash chromatography (1:20 → 1:4 Et_2O−PE) gave 1.33 g (76%) of crystalline **6h**: mp 71−72 °C; $[\alpha]^{22}_D$ −203.7° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69−1.92 (m, 4H), 2.67−2.72 (m, 1H), 2.94 (dd, 1H, *J* = 16.4, 5.0 Hz), 3.09−3.10 (m, 1H), 3.12 (s, 3H), 3.20 (dd, 1H, *J* = 9.3, 3.7 Hz), 3.23−3.30 (m, 2H), 3.92 (dd, 1H, *J* = 16.4, 9.1 Hz), 4.39 (m, 1H), 6.71 (d, 1H, *J* = 3.6 Hz), 7.22−8.01 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 26.6, 42.4, 44.2, 49.4, 58.8, 62.9, 74.4, 126.6, 128.1, 128.3, 128.5, 132.5, 136.7, 137.5, 142.6, 198.7; IR (KBr, cm^{-1}) 2826, 1665, 1597; mass spectrum *m*/*z* (rel intensity) 350 M^+ (9), 305 (18), 70 (100). Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.11; H, 6.24; N, 7.74.

(2*S*)-2-(Methoxymethyl)-1-[[(1*R*)-4-oxo-2-phenyl-3-pentylidene]amino]pyrrolidine (6i). From **2i**, flash chromatography (1:4 → 1:2 Et_2O−PE) gave 0.86 g (60%) of **6i** as an oil: $[\alpha]^{22}_D$ −179.0° (*c* 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.73−2.02 (m, 4H), 2.18 (s, 3H), 2.56 (dd, 1H, *J* = 16.3, 5.4 Hz), 2.69−2.77 (m, 1H), 3.21 (dd, 1H, *J* = 16.3, 9.2 Hz), 3.24−3.30 (m, 1H), 3.34−3.50 (m, 2H), 3.37 (s, 3H), 3.54 (dd, 1H, *J* = 8.5, 3.2 Hz), 4.13 (ddd, 1H, *J* = 9.0, 5.2, 3.7 Hz), 6.64 (d, 1H, *J* = 3.6 Hz), 7.19−7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 26.6, 30.5, 44.1, 47.4, 49.6, 59.1, 63.1, 74.7, 126.6, 127.9, 128.5, 137.0, 142.3, 207.4; IR (film, cm^{-1}) 2878, 1715, 1601; mass spectrum *m*/*z* (rel intensity) 288 M^+ (20), 243 (100). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.64; H, 8.17; N, 9.33.

Synthesis of 4-Oxo Aldehydes 7. Method A. Dry ozone was bubbled through a cooled (−78 °C) solution of hydrazone **4** or **6** (1 mmol) in CH_2Cl_2 (6 mL) until appearance of a permanent blue color. After addition of Me_2S (1 mL, 13.6 mmol), the mixture was allowed to reach rt and concentrated, and the residue was purified by flash chromatography.

Method B. To a cooled (0 °C) solution of hydrazone **4** or **6** (1 mmol) in Et_2O (30 mL) was added 5 N HCl (10 mL), and the mixture was vigorously stirred until TLC indicated total consumption of the starting material (ca. 10 min). The aqueous layer was extracted with Et_2O several times (each 10 mL) until the product could no longer be detected (TLC). The combined organic layers were neutralized ($NaHCO_3$, s, 0.1 g), dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography.

The methods followed for deprotection, chromatography eluants, yields, and spectral and analytical data for compounds **7b**,**c**,**e**−**i** are as follows.

1-Methyl-3-oxocyclopentanecarbaldehyde (*rac*-7b). From **4b**, following method B, flash chromatography (1:1 Et_2O−PE) gave 107 mg (85%) of **7b** as an oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.78−1.88 (m, 1H), 2.03 (d, 1H, *J* = 18.3 Hz), 2.25−2.40 (m, 3H), 2.67 (d, 1H, *J* = 18.3 Hz), 9.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 30.0, 36.1, 45.2, 50.6, 202.4, 215.8; IR (film, cm^{-1}) 2724, 1742; mass spectrum *m*/*z* (rel intensity) 126 M^+ (8), 98 (100). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.55; H, 8.06.

(*R*)-1-Methyl-3-oxocyclopentanecarbaldehyde [(*R*)-7b]. From **6b**, following method B, flash chromatography (1:1 Et_2O−PE) gave 110 mg (87%) of (*R*)-**7b** as an oil: $[\alpha]^{22}_D$ −22.0° (*c* 1, $CHCl_3$). Spectral and analytical data were as for the racemic **7b** described above.

(1*R*,2*R*)-2-Methyl-3-oxocyclopentanecarbaldehyde [(*R*,*R*)-7c]. From **6c**, following method A, flash chromatography (1:2 Et_2O−PE) gave 118 mg (94%) of (*R*,*R*)-**7c** as an oil: $[\alpha]^{22}_D$ +82.3° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.17 (d, 3H, *J* = 7.0 Hz), 1.93−2.01 (m, 1H), 2.21−2.33 (m, 2H), 2.39−2.52 (m, 2H), 2.68−2.75 (m, 1H), 9.78 (d, 1H, *J* = 2.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 21.1, 36.1, 44.4, 56.2, 201.0, 217.1; IR (film, cm^{-1}) 2882, 1744, 1657; mass spectrum *m*/*z* (rel intensity) 126 M^+ (19), 98 (55), 69 (100). Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.30; H, 8.11.

(*R*)-1-Methyl-3-oxocyclohexanecarbaldehyde [(*R*)-7e]. From **6e**, following method B, flash chromatography (4:1 Et_2O−PE) gave 97 mg (69%) of (*R*)-**7e** as an oil: $[\alpha]^{22}_D$ +5.5°

(*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[40]

2,2-Dimethyl-5-oxocyclohexanecarbaldehyde (*rac*-7f). From **4f**, following method B, flash chromatography (1:3 Et_2O−PE) gave 109 mg (71%) of known[41] crystalline **7f**.

(*R*)-2,2-Dimethyl-5-oxocyclohexanecarbaldehyde [(*R*)-7f]. From **6f**, following method B, flash chromatography (1:6 Et_2O−PE) gave 120 mg (78%) of crystalline (*R*)-**7f**: mp 86−87 °C; $[\alpha]^{22}_D$ +34.3° (*c* 1, $CHCl_3$). Following method A, flash chromatography (1:6 Et_2O−PE) gave 106 mg (69%) of crystalline (*R*)-**7f**: mp 86−88 °C; $[\alpha]^{22}_D$ +34.1° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[41]

***cis*-2-*tert*-Butyl-5-oxocyclohexanecarbaldehyde [(*rac*)-7g].** From **4g**, following method A, flash chromatography (1:1 Et_2O−PE) gave 137 mg (75%) and, following method B, flash chromatography (2:1 Et_2O−PE) gave 147 mg (81%) of **7g** as an oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (s, 9H), 1.58−1.68 (m, 1H), 1.98−2.06 (m, 3H), 2.34−2.39 (m, 1H), 2.36 (dd, 1H, J = 16.5, 6.5 Hz), 2.63 (dd, 1H, J = 16.4, 3.8 Hz), 2.84−2.87 (m, 1H), 9.63 (d, 1H, J = 1.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 27.0, 33.8, 36.8, 38.1, 41.9, 46.8, 201.7, 210.1; IR (film, cm^{-1}) 2891, 1726; mass spectrum *m*/*z* (rel intensity) 182 M^+ (1), 57 (100); *m*/*z* calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1304.

4-Oxo-2,4-diphenylbutanal [(*rac*)-7h]. From **4h**, following method B, flash chromatography (1:10 Et_2O−PE) gave 210 mg (88%) of known[42] crystalline **7h**.

(*R*)-4-Oxo-2,4-diphenylbutanal [(*R*)-7h]. From **6h**, following method A, flash chromatography (1:20 Et_2O−PE) gave 186 mg (78%) of crystalline (*R*)-**7h**: mp 59−60 °C; $[\alpha]^{22}_D$ −55.6° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[42]

2-Phenyl-4-oxopentanal [(*rac*)-7i]. From **4i**, following method B but with 3 mmol of 5 N HCl (0.6 mL), flash chromatography (1:5 Et_2O−PE) gave 132 mg (75%) of known[43] **7i** as an oil.

(*R*)-2-Phenyl-4-oxopentanal [(*R*)-7i]. From **6i**, following method B, flash chromatography (1:6 → 1:4 Et_2O−PE) gave 155 mg (88%) of (*R*)-**7i** as an oil: $[\alpha]^{22}_D$ −41.6° (*c* 1, $CHCl_3$). Following method A, flash chromatography (1:6 Et_2O−PE) gave 127 mg (72%) of (*R*)-**7i**: $[\alpha]^{22}_D$ −39.5° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[43]

Synthesis of 4-Oxo Nitriles 8. To a cooled (0 °C) solution of 4-oxo hydrazone **4** or **6** (1 mmol) in CH_3OH (10 mL) was added dropwise a suspension of MMPP·6 H_2O (1.24 g, 2.50 mmol), and the mixture was stirred until consumption of the starting material (ca. 5 min). The mixture was then diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (20 mL). The organic layer was washed with brine (2 × 20 mL) and H_2O (20 mL), dried ($MgSO_4$), and concentrated, and the residue purified by flash chromatography. Eluants, yields, and spectral and analytical data for compounds **8a**−**i** are as follows.

3-Oxocyclopentanecarbonitrile [(*rac*)-8a]. From **4a**, flash chromatography (1:1 Et_2O−PE) gave 99 mg (91%) of known[44] **8a** as an oil.

(*R*)-3-Oxocyclopentanecarbonitrile [(*R*)-8a]. From **6a**, flash chromatography (1:1 Et_2O−PE) gave 98 mg (90%) of (*R*)-**8a** as an oil: $[\alpha]^{22}_D$ +35.3° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[44]

1-Methyl-3-oxocyclopentanecarbonitrile [(*rac*)-8b]. From **4b**, flash chromatography (1:1 Et_2O−PE) gave 106 mg (86%) of known[45] **8b** as an oil.

(*R*)-1-Methyl-3-oxocyclopentanecarbonitrile [(*R*)-8b]. From **6b**, flash chromatography (1:1 Et_2O−PE) gave 120 mg (98%) of (*R*)-**8b** as an oil: $[\alpha]^{22}_D$ −54.2° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[45]

(1*R*,2*R*)-2-Methyl-3-oxocyclopentanecarbonitrile [(*R*,*R*)-8c]. From **6c**, flash chromatography (1:2 Et_2O−PE) gave 86 mg (70%) of crystalline (*R*,*R*)-**8c**: mp 55−57 °C (lit.[36] mp 55 °C); $[\alpha]^{22}_D$ +63.6° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic compound.[36] The minor isomer was not isolated.

3-Oxocyclohexanecarbonitrile [(*rac*)-8d]. From **4d**, flash chromatography (3:1 Et_2O−PE) gave 116 mg (94%) of known **8d**[46] as an oil.

(*R*)-1-Methyl-3-oxocyclohexanecarbonitrile [(*R*)-8e]. From **6e**, flash chromatography (1:1 Et_2O−PE) gave 119 mg (87%) of (*R*)-**8e** as an oil: $[\alpha]^{22}_D$ −24.3° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic compound.[47]

2,2-Dimethyl-5-oxocyclohexanecarbonitrile [(*rac*)-8f]. From **4f**, flash chromatography (1:2 Et_2O−PE) gave 138 mg (91%) of known[41] crystalline **8f**.

(*S*)-2,2-Dimethyl-5-oxocyclohexanecarbonitrile [(*S*)-8f]. From **6f**, flash chromatography (1:6 Et_2O−PE) gave 126 mg (83%) of crystalline (*S*)-**8f**: mp 63−64 °C; $[\alpha]^{22}_D$ −11.7° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic compound.[41]

***cis*-2-*tert*-Butyl-5-oxocyclohexanecarbonitrile [(*rac*)-8g].** From **4g**, flash chromatography (1:1 Et_2O−PE) gave 154 mg (86%) of known *cis*-**8g**[37] as an oil.

4-Oxo-2,4-diphenylbutanenitrile [(*rac*)-8h]. From **4h**, flash chromatography (1:20 Et_2O−PE) gave 212 mg (90%) of known[48] crystalline **8h**.

(*R*)-4-Oxo-2,4-diphenylbutanenitrile [(*R*)-8h]. From **6h**, flash chromatography (1:20 Et_2O−PE) gave 223 mg (95%) of crystalline (*R*)-**8h**: mp 64−65 °C; $[\alpha]^{22}_D$ +16.2° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic compound.[48]

2-Phenyl-4-oxopentanenitrile [(*rac*)-8i]. From **4i**, flash chromatography (1:3 Et_2O−PE) gave 158 mg (91%) of crystalline **8i**: mp 63−64 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 3.03 (dd, 1H, J = 18.0, 6.2 Hz), 3.25 (dd, 1H, J = 18.0, 7.9 Hz), 4.40 (dd, 1H, J = 7.9, 6.2 Hz), 7.38−7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.8, 31.4, 48.6, 120.3, 127.2, 128.3, 129.2, 134.9, 203.0; IR (KBr, cm^{-1}) 2236, 1704; mass spectrum *m*/*z* (rel intensity) 173 M^+ (43), 130 (100). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.11; H, 6.24; N, 7.74.

(*R*)-2-Phenyl-4-oxopentanenitrile [(*R*)-8i]. From **6i**, flash chromatography (1:4 → 1:2 Et_2O−PE) gave 157 mg (91%) of crystalline (*R*)-**8i**: mp 63−64 °C; $[\alpha]^{22}_D$ +8.1° (*c* 1, $CHCl_3$). Spectral and analytical data were as for the racemic **8i** described above.

Synthesis of 4-Oxo Carboxylic Acids 9. Method A. Hydrazone **4** or **6** (1 mmol) was treated with HCl as for aldehydes **7**. After neutralization, the combined organic layers were concentrated to a volume of ca. 10 mL. The solution was then cooled to −30 °C and treated with a solution of the Jones reagent (10 mL, 6.7 mmol). The reaction mixture was allowed to warm to rt and then stirred for 10 min. The mixture was filtered through a short silica gel column and eluted with Et_2O until the product could no longer be detected (TLC). The filtrate was then concentrated *in vacuo* and the residue dissolved in 1 M NaOH (10 mL) and washed with Et_2O (2 × 10 mL). The aqueous phase was acidified with 2 N H_2SO_4 and extracted with ethyl acetate (7 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography.

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Method B. A solution of hydrazone **6** (1 mmol) in Et_2O (10 mL) cooled to −30 °C was treated with a solution of the Jones reagent (15 mL, 10 mmol). The reaction mixture was allowed to warm to rt and then stirred for 10 min. The mixture was filtered through a short silica gel column and eluted with Et_2O until the product could no longer be detected (TLC). The filtrate was then concentrated *in vacuo* and the residue dissolved in 1 M NaOH (10 mL) and washed with Et_2O (2 × 10 mL). The aqueous phase was acidified with 2 N H_2SO_4 and extracted with ethyl acetate (7 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography.

Method C. Dry ozone was bubbled through a cooled (−78 °C) solution of hydrazone **4** (1 mmol) in acetone (25 mL) until appearance of a permanent blue color. The solution was then treated with a solution of the Jones reagent (15 mL, 10 mmol), and the reaction mixture was allowed to warm to rt and concentrated. The residue was dissolved in 1 M NaOH (10 mL) and washed with Et_2O (2 × 10 mL). The aqueous phase was acidified with 2 N H_2SO_4 and extracted with ethyl acetate (7 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated, giving the pure product. Eluants, yields, and spectral and analytical data for compounds **9** are as follows:

3-Oxocyclopentanecarboxylic Acid (*rac*-9a). Following method C, use of **4a** yielded pure **9a** (119 mg, 93%). Spectral and analytical data were in good agreement with those reported.[31]

(*R*)-3-Oxocyclopentanecarboxylic Acid [(*R*)-9a]. Following method A from **6a**, flash chromatography (1:4 Et_2O−PE) gave 108 mg of (*R*)-**9a** (84%) as an oil: $[\alpha]^{22}_D$ +21.8° (*c* 1.9, CH_3OH) [lit.[31] $[\alpha]^{21}_D$ +22.1° (*c* 1.9, CH_3OH)]. Spectral data were in good agreement with those previously reported.[31]

(1*R*,2*R*)-2-Methyl-3-oxocyclopentanecarboxylic Acid [(*R*,*R*)-9c]. Following method B from **6c**, flash chromatography (1:1 Et_2O−PE) gave 39 mg (28%) of crystalline (*R*,*R*)-**9c**: mp 84−86 °C; $[\alpha]^{22}_D$ +66.6° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (d, 3H, J = 7.0 Hz), 2.04 (dtd, 1H, J = 12.5, 10.9, 8.7 Hz), 2.23 (ddd, 1H, J = 19.0, 11.0, 9.0 Hz), 2.36 (dddd, 1H, J = 12.5, 8.7, 6.7, 1.9 Hz), 2.42−2.50 (m, 1H), 2.51 (ddt, 1H, J = 18.8, 8.8, 1.7 Hz), 2.70 (td, 1H, J = 11.0, 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.1, 24.2, 36.6, 47.3, 48.7, 179.6, 217.4; IR (KBr, cm^{-1}) 3380−2810, 1734, 1717; mass spectrum *m*/*z* (rel intensity) 142 M^+ (68), 97 (58), 69 (100). Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.08; H, 7.22.

3-Oxocyclohexanecarboxylic Acid (*rac*-9d). Following method C, use of **4d** yielded pure **9d** (131 mg, 92%). Spectral and analytical data were in good agreement with those previously reported.[49]

(*R*)-1-Methyl-3-oxocyclohexanecarboxylic Acid [(*R*)-9e]. Following method B from **6e**, flash chromatography (1:1 Et_2O−PE) gave 72 mg (46%) of (*R*)-**9e** as an oil: $[\alpha]^{22}_D$ −14.0° (*c* 1, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[47]

(*S*)-2,2-Dimethyl-5-oxocyclohexanecarboxylic Acid [(*S*)-9f]. Following method B from **6f**, flash chromatography (1:2 Et_2O−PE) gave 109 mg (64%) of crystalline (*S*)-**9f**: mp 103−104 °C; $[\alpha]^{22}_D$ +18.8° (*c* 0.8, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[41]

(*R*)-4-Oxo-2,4-diphenylbutyric Acid [(*R*)-9h]. Following method B from **6h**, flash chromatography (1:4 → 1:1 Et_2O−PE) gave 79 mg (31%) of crystalline (*R*)-**9h**: mp 161−162 °C; $[\alpha]^{22}_D$ −92.9° (*c* 1.2, $CHCl_3$). Spectral and analytical data were in good agreement with those reported for the racemic form.[50]

Synthesis of (2*R*,3*R*)-2,3-Butanediol-Derived Ketals 10. To a solution of ketone **8** (1 mmol) and (2*R*,3*R*)-2,3-butanediol (0.18 mL, 2 mmol) in dry benzene (25 mL) was added *p*-TsOH (cat.), and the mixture was refluxed with azeotropic removal of water until TLC indicated total consumption of the starting material (ca. 1 h). The mixture was then neutralized ($NaHCO_3$, solid), concentrated, and purified by flash chromatography. Eluants, yields, and spectral and analytical data for compounds **10** are as follows:

10a. By use of **8a**, flash chromatography (1:6 → 1:1 Et_2O−PE) gave 154 mg (85%) of crystalline **10a**: mp 34−35 °C; $[\alpha]^{22}_D$ −18.2° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23−1.26 (m, 6H), 1.81−1.87 (m, 1H), 1.95−2.03 (m, 2H), 2.09 (dd, 1H, J = 13.5, 9.8 Hz), 2.16−2.25 (m, 1H), 2.23 (ddd, 1H, J= 13.5, 8.2, 1.0 Hz), 2.81−2.88 (m, 1H), 3.53−3.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.4, 16.5, 25.2, 28.0, 36.3, 41.4, 78.3, 78.5, 114.8, 121.9; IR (KBr, cm^{-1}) 2239; mass spectrum *m*/*z* (rel intensity) 181 M^+ (11), 153 (100). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 65.96; H, 8.46, N, 7.63.

10e. By use of **8e**, flash chromatography (1:4 Et_2O−PE) gave 184 mg (88%) of **10e** as an oil: $[\alpha]^{22}_D$ −45.1° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (d, 3H, J = 5.5 Hz), 1.25−1.32 (m, 1H), 1.28 (d, 3H, J = 5.6 Hz), 1.40 (s, 3H), 1.43−1.48 (m, 1H), 1.50 (d, 1H, J = 13.5 Hz), 1.70−1.77 (m, 2H), 1.85−1.92 (m, 1H), 1.93−1.98 (m, 1H), 2.05 (dt, 1H, J = 13.5, 1.9 Hz), 3.58−3.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.8, 20.6, 27.7, 33.5, 35.4, 36.4, 45.9, 78.0, 78.7, 106.1, 124.3; IR (film, cm^{-1}) 2236; mass spectrum *m*/*z* (rel intensity) 209 M^+ (23), 127 (100). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.57; H, 9.17, N, 6.73.

10f. By use of **8f**, flash chromatography (1:20 → 1:6 Et_2O−PE) gave 172 mg (77%) of **10f** as an oil: $[\alpha]^{22}_D$ −38.1° (*c* 1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.12 (s, 3H), 1.20−1.24 (m, 6H), 1.47 (ddd, 1H, J = 13.7, 4.7, 3.4 Hz), 1.54 (td, 1H, J = 13.6, 3.9 Hz), 1.58−1.62 (m, 1H), 1.71 (td, 1H, J = 13.4, 4.7 Hz), 1.87−1.92 (m, 2H), 2.68 (dd, 1H, J = 9.9, 7.0 Hz), 3.57−3.65 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.4, 16.7, 20.0, 29.6, 31.9, 32.4, 35.2, 35.6, 37.7, 78.0, 78.2, 105.8, 120.4; IR (film, cm^{-1}) 2236; mass spectrum *m*/*z* (rel intensity) 223 M^+ (4), 127 (100) Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.16; H, 9.59, N, 6.17

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3a**, **3a′**, **3d**, **3d′**, **3f**, **3g**, **3h**, **3h′**, **4a**, **4b**, **4f**, **5b**, **5c**, **6a**, and **7g** (35 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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