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Selective 1,5-Alkylidenecarbene Insertion Reactions on [3.2.1] Oxabicyclic Ethers: A New Approach toward the AB Ring System of Ingenol

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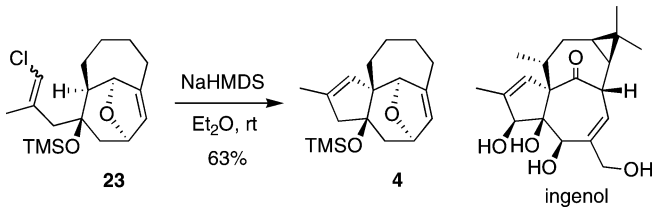
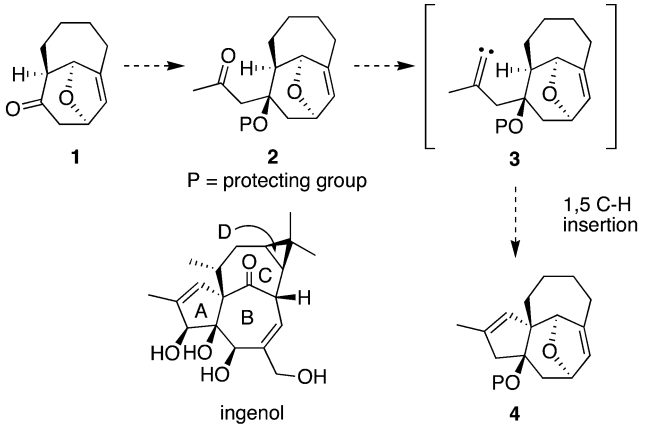
ABSTRACT



Two methods to achieve the formal aldol reaction between acetone and two oxabicyclic [3.2.1] ketones are reported. The trimethylsilyl-protected β-hydroxy ketones are converted by a Wittig reaction into vinyl chlorides as synthetic precursors to alkylidenecarbenes. Selective 1,5 C–H over 1,5 O–Si insertion has been applied to the synthesis of a model for the ABC ring system of ingenol.

Alkylidenecarbenes, or alkenylidenes, are versatile intermediates for organic synthesis.[1] We are interested in the selective 1,5 C−H insertion of alkylidenecarbenes as a means to construct the A-ring of ingenol (Scheme 1).[2,3] Two particular features of the 1,5 C−H insertion reaction appear to be particularly attractive in this context. First, alkylidenecarbenes are known to selectively insert into tertiary over secondary C−H bonds.[4] Second, the reaction has been shown to proceed with retention of configuration at the C−H bond at a stereocenter.[5] This we deem particularly important in terms of the trans BC ring junction of ingenol, which has been shown to be both thermodynamically less favorable than the cis configuration and also critical for the biological

Scheme 1. Alkylidenecarbene Insertion Strategy



(1) For a review of early work, see: Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164.

(2) For recent representative examples of 1,5 C−H insertion reactions of alkylidenecarbenes, see: (a) Ohira, S.; Fujiwara, H.; Maeda, K.; Habara, M.; Sakaedani, N.; Akiyama, M.; Kuboki, A. *Tetrahedron Lett.* **2004**, *45*, 1639. (b) Taber, D. F.; Storck, P. H. *J. Org. Chem.* **2003**, *68*, 7768. (c) Feldman, K. S.; Saunders, J. C.; Wrobleski, M. L. *J. Org. Chem.* **2002**, *67*, 7096. (d) Green, M. P.; Prodger, J. C.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6609. (e) Wardrop, D. J.; Zhang, W. *Tetrahedron Lett.* **2002**, *43*, 5389. (f) Bradley, D. M.; Mapitse, R.; Thomson, N. M.; Hayes, C. J. *J. Org. Chem.* **2002**, *67*, 7613. (g) Walker, L. F.; Bourghida, A.; Connolly, S.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 965. (h) Worden, S. M.; Mapitse, R.; Hayes, C. J. *Tetrahedron Lett.* **2002**, *43*, 6011. (i) Ohira, S.; Kuboki, A.; Hasegawa, T.; Kikuchi, T.; Kutsukake, T.; Nomura, M. *Tetrahedron Lett.* **2002**, *43*, 4641. (j) Taber, D. F.; Neubert, T. D. *J. Org. Chem.* **2001**, *66*, 143. For other methods for C−H bond activation, see: (k) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900 and references therein.

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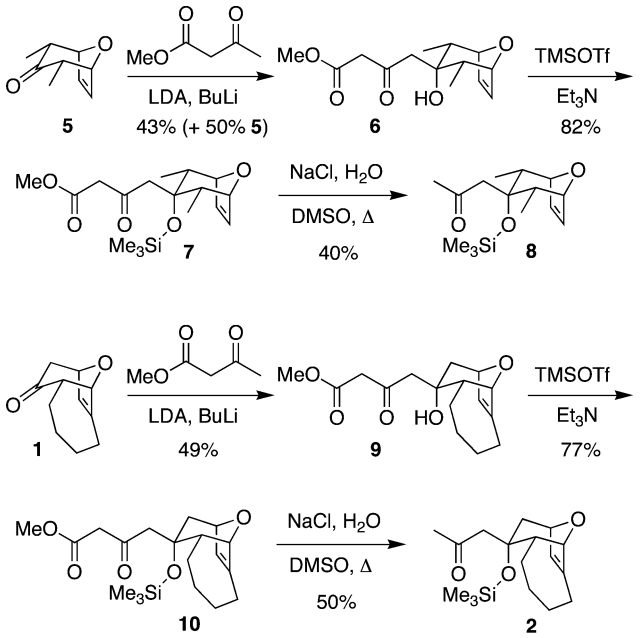
activity of the natural product.[6] Any strategy therefore that establishes this stereochemical feature must also be coupled with a compatible method for installing the A-ring. Herein we report the first examples of alkylidenecarbene 1,5 C−H insertion chemistry on the [3.2.1] oxabicyclic skeleton as models for the AB ring system of ingenol, an approach that also overrides the "usual" preference for alkylidenecarbenes to undergo 1,5 O−Si insertion over 1,5 C−H insertion.[7]

We have recently reported the synthesis of oxatricyclic ketone **1** as a model for the BC ring system of ingenol, where it is anticipated that stereoselective reduction of the alkene offers a potential route to the *trans*-ring junction (Scheme 1).[3k] Installation of the A-ring onto this system can in principle be achieved by a selective 1,5 C−H insertion reaction of an alkylidenecarbene **3** into the tertiary axial C−H bond over the axial or equatorial secondary C−H bonds. Alkylidenecarbene **3** could be generated from ketone **2**, the product of a face-selective aldol reaction between ketone **1** and the enolate of acetone, followed by protection of the alcohol. However, while such an approach can deliver the requisite bridgehead oxygen at the AB ring juncture, it also opens up the possibility of an alternative undesired reaction pathway, formal insertion of the alkylidenecarbene into the O−P bond leading to dihydrofuran formation. Although such a reaction pathway is generally favored over the 1,5 C−H insertion pathway,[7] we felt that structural features present in **3** might disfavor this pathway sufficiently to warrant further investigation (vide infra).

Addition of nucleophiles to [3.2.1] oxabicyclic ketones has been extensively investigated. In general, preferential addition syn to the oxygen bridge is observed.[8] We are not aware, however, of any examples of direct enolate addition to such ketones. Taking the readily prepared **5** as a representative oxabicyclic ketone,[9] a number of attempts were made to add the enolate of acetone[10] under various conditions, without success. A more reactive enolate in the form of the dianion of methyl acetoacetate could be added, although the yields were only moderate (Scheme 2).[11] β-Keto ester **6** could be protected and decarboxylated to provide ketone **8**.[12]

Scheme 2. Addition of Dienolates to Oxabicyclic Ketones



An identical sequence of reactions on oxatricyclic ketone **1** gave the protected β-hydroxy ketone **2**, albeit again in only moderate yield.

The low yield for the enolate addition step in the above reaction made us consider alternative strategies based on addition of a suitable organometallic reagent that could subsequently be converted into an alkylidenecarbene precursor such as a vinyl halide. Taber has reported a bromination−dehydrobromination strategy for the conversion of terminal alkenes to vinylbromides.[13]

Toward this end, we added 2-methylallyl Grignard to ketones **5** and **1** at −78 °C to give the axial alcohols **11** and **13**, respectively (Scheme 3). However, selective bromination of the terminal alkene (Br_2, Et_2O, −78 °C) was thwarted by the higher reactivity of the internal alkene. Although ultimately not suitable for our purpose, this reactivity could be exploited for high-yielding syntheses of the unusual bromoethers **12** and **14**, which also pointed to the close

(3) Total syntheses of ingenol: (a) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726. (b) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, *125*, 1498. For a review of approaches to the synthesis of ingenol, see: (c) Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387. For more recent work, see: (d) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032. (e) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett.* **1998**, *39*, 2265. (f) Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296. (g) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett.* **2000**, *41*, 3927. (h) Tang, H.; Yusuff, N.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1563. (i) Rigby, J. H.; Bazin, B.; Meyer, J. H.; Mohammadi, F. *Org. Lett.* **2002**, *4*, 799. (j) Mislin, G. L.; Miesch M. *J. Org. Chem.* **2003**, *68*, 433. (k) Grainger, R. S.; Owoare, R. B.; Tisselli, P.; Steed, J. W. *J. Org. Chem.* **2003**, *68*, 7899.

(4) Relative rates of insertion methine > methylene > methyl can be influenced by the presence of adjacent heteroatoms and by the method used to generate the alkylidenecarbene. See, for example: Taber, D. F.; Christos, T. E. *Tetrahedron Lett.* **1997**, *38*, 4927.

(5) (a) Gilbert, J. C.; Giamalva, D. H.; Weerasooriya, U. *J. Org. Chem.* **1983**, *48*, 5251. (b) Gilbert, J. C.; Giamalva, D. H.; Baze, M. E. *J. Org. Chem.* **1985**, *50*, 2557.

(6) A highly functionalised cis-fused analogue of ingenol has been shown to be devoid of biological activity: Paquette, L. A.; Ross, R.; Springer, J. *J. Am. Chem. Soc.* **1988**, *110*, 6192.

(7) (a) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 461. (b) Kim, S.; Cho, C. M. *Tetrahedron Lett.* **1995**, *36*, 4845. (c) Feldman, K. S.; Wrobleski, M. L. *J. Org. Chem.* **2000**, *65*, 8659. (d) Hobley, G. H.; Stuttle, K.; Wills, M. *Tetrahedron* **2003**, *59*, 4739. (e) Gais, H.-J.; Reddy, L. R.; Babu, G. S.; Raabe, G. *J. Am. Chem. Soc.* **2004**, *126*, 4859. See also ref 2c.

(8) (a) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (b) Chiu, P.; Lautens, M. In *Topics in Current Chemistry*; Metz, P., Ed.; Springer-Verlag: New York, 1997; Vol. 190, pp 1−85. (c) Hartung, I. V.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2004**, *43*, 1934.

(9) Lautens, M.; Bouchain, G. *Org. Synth.* **2002**, *79*, 251.

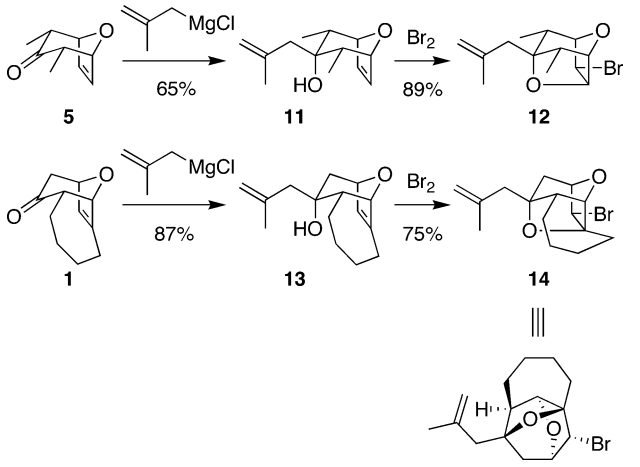
(10) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Basbas, C. F., III. *J. Am. Chem. Soc.* **1999**, *121*, 7283.

(11) While this manuscript was being prepared, Chiu reported the high-yielding addition of the dianion of ethylacetoacetate to oxabicyclic ketone **5**: Chiu, P.; Zhang, X.; Ko, R. Y. Y. *Tetrahedron Lett.* **2004**, *45*, 1531.

(12) Attempted decarboxylation prior to protection results in reformation of ketone **5**.

(13) Taber, D. F.; Christos, T. E.; Neubert, T. D.; Batra, D. *J. Org. Chem.* **1999**, *64*, 9673.

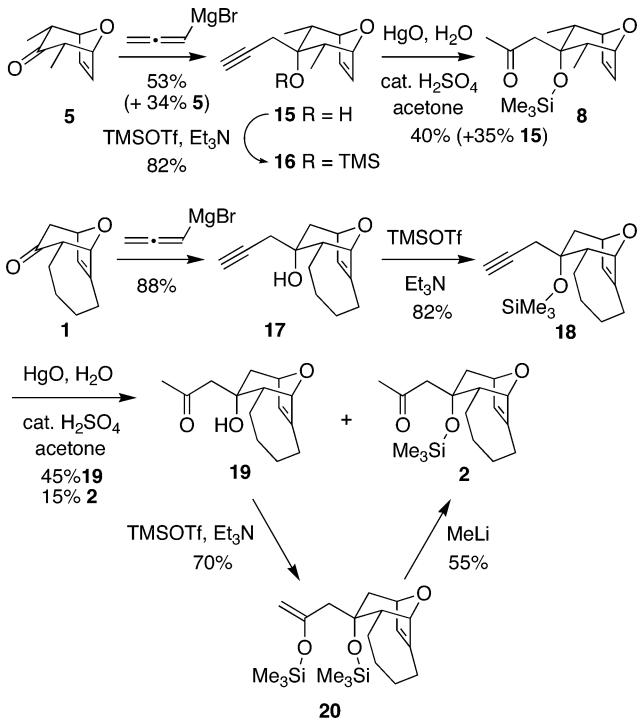
Scheme 3. Intramolecular Haloetherification



proximity of the axial-orientated alcohol to the internal double bond.[14] Interestingly, compound **14** contains a trans arrangement in the [4.4.1] carbocyclic system.

Addition of allenyl Grignard[15] was also successful (Scheme 4). After protection of the alcohol as a trimethylsilyl ether,

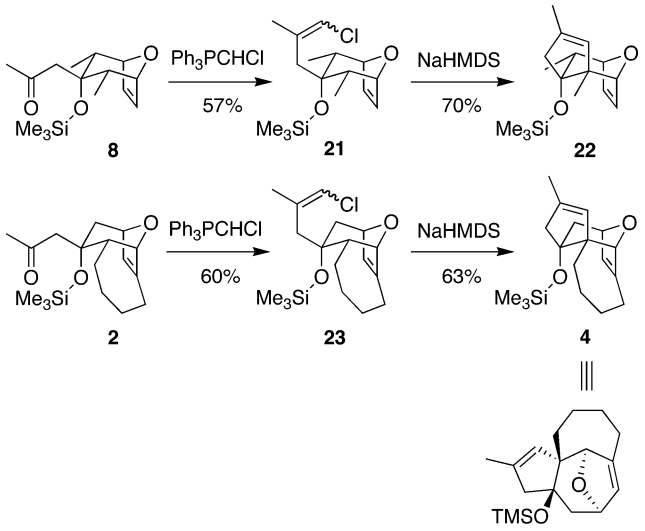
Scheme 4. Formation of β-Silyloxyketones via Alkyne Hydrolysis



selective hydrolysis of the terminal alkyne could be achieved,[16] although this reaction was accompanied by significant amounts of silyl deprotection in the case of the tricyclic system **18**. Reprotection of the β-hydroxyketone **19** under standard conditions gave the doubly silylated product **20**. Attempts to limit the formation of **20** by reducing the equivalents of TMSOTf showed that silylenol ether formation could not be suppressed, pointing to the sterically hindered nature of the alcohol group in these compounds. Preliminary results suggest that the bis-silylated compound **20** can be selectively converted to the required silyl ether **2** using methyllithium to generate the corresponding enolate, followed by quenching with water.[17]

Wittig reaction of protected β-hydroxyketones **8** and **2** with (chloromethyl)triphenylphosphonium chloride ylid gave approximately 1:1 mixtures of geometrical chloroalkenes **21** and **23**, respectively (Scheme 5). The stereochemistry of

Scheme 5. 1,5 C−H Alkylidenecarbene Insertion Reactions



these chloroalkenes proved to be irrelevent: both isomers gave rise to the same product of 1,5 C−H alkylidenecarbene insertion (cyclopentenes **22** and **4**, respectively) upon exposure to sodium bis(trimethylsilyl)amide at room temperature in diethyl ether.[18] In the case of chloroalkene **23**, complete selectivity for insertion into a tertiary axial C−H bond over a secondary axial or equatorial C−H bond is observed.

Alkylidenecarbenes are known to undergo intramolecular 1,5 O−Si insertion reactions to yield 2,3-dihydrofuran derivatives, and this pathway has been shown to proceed more rapidly than 1,5 C−H insertion.[7,19] Notably in the case of both **21** and **23**, we have not observed any products arising from this potentially competing reaction. The mechanism of such reactions can proceed via two possible pathways,

(14) Stereochemistry of **12** and **14** are assigned on the basis of attack of Br_2 on the less hindered *exo*-face of the internal alkene, followed by intramolecular capture of the bromonium ion intermediate by the axial alcohol.

(15) Hopf, H.; Böhm, I.; Kleinschroth, J. *Org. Synth.* **1981**, *60*, 41−48.

(16) Jacobi, P. A.; Herradura, P. *Tetrahedron Lett.* **1997**, *38*, 6621.

(17) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.

(18) Geometrical chloroalkenes are separable in the case of **21**. We have observed that (*E*)-**21** cyclizes faster than (*Z*)-**21** under identical reaction conditions.

(19) An exception is seen in the work of Wills, whereby 1,5 C−H insertion into the activated methylene of a benzylic ether is preferred over 1,5 O-TBS insertion. However, a MOM methylene CH is less likely to undergo insertion than an O-TBS. See ref 7d.

concerted O−Si insertion or, more likely, an initial interaction of the vacant orbital on the carbene with an oxygen lone pair to produce a transient oxonium ylide,[20] which undergoes a subsequent 1,2 silyl migration. Should the latter indeed be the case, then the absence of products derived from 1,5 O−Si insertion can be ascribed to the need to adopt an unfavorable conformation **I** or **III** in order to achieve orbital overlap (Figure 1, illustrated for the case of **21**). In particular, the

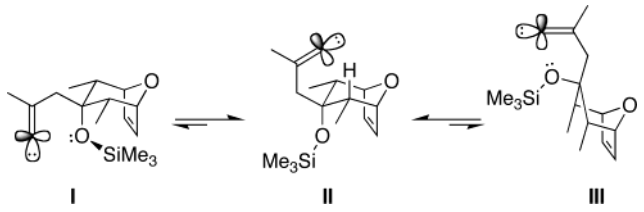


Figure 1. Conformational control of 1,5 alkylidenecarbene insertion.

bulky trimethylsilyl group is expected to be orientated *exo* to the oxabicyclic ring system in the lowest energy conformation **II**, placing the lone pairs on oxygen in an *endo* orientation where they are unable to interact with the alkylidenecarbene and hence allowing the 1,5 C−H insertion pathway to dominate.[21]

In conclusion, two methods for the preparation of alkylidenecarbene precursors based on nucleophilic attack on [3.2.1] oxabicyclic ketones have been developed. Selective insertion into a bridgehead tertiary C−H bond has been used to generate a model for the ABC ring system of ingenol and more generally for the preparation of cis-fused perhydrozulenes. Further studies on incorporating this chemistry in a synthesis of a trans intrabridgehead ring system related to ingenol are ongoing.

Acknowledgment. We thank EPSRC and King's College London for funding this work and AstraZeneca and Pfizer for additional financial support.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all new compounds prepared in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

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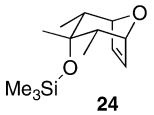
(20) Sueda T.; Nagaoka, T.; Goto, S.; Ochiai, M. *J. Am. Chem. Soc.* **1996**, *118*, 10141.

(21) We have carried out molecular mechanics calculations on the simplified model compound **24** using the Sybyl force field in Spartan IBM Version 5.1.3 X11 (Wavefunction, Inc). Geometry optimization for both chair and boat conformations show the lowest energy boat conformation to be 7.9 kcal/mol higher in energy than the chair. In both cases, the trimethylsilyl group is orientated gauche to the methyl group around the carbon−oxygen bond (CH_3−C−O−Si dihedral angle 51.1° for chair and 52.2° for boat). Rotation about this carbon−oxygen bond in the chair form shows a conformation where the lone pair and methyl group are synperiplanar to be 6.1−6.5 kcal/mol higher in energy than the lowest energy gauche conformation. Similarly, in the boat form, the synperiplanar orientation of methyl and the oxygen lone pair is 5.5 kcal/mol higher in energy than the gauche conformation.



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