On the reaction of lithium diisopropylamide with .pi.-deficient heteroaromatics. A single electron transfer mechanism

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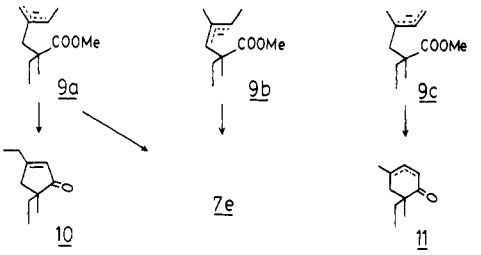
Scheme II

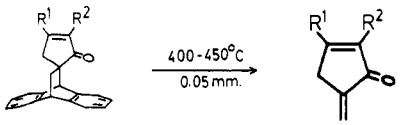


As summarized in Table I, if R^2 = aryl, spirocyclopentenone **7** was isolated as the only product (entries **a–d**). However, if $R^2 \neq$ aryl, the two products **7** and **8** were isolated in almost equal amounts (entries **f** and **g**). These spiro ketones **7** and **8** can be separated by TLC [silica gel plates, with ethyl acetate/hexane (10:1) as the eluent] and are easily distinguished by their spectroscopic data.[10]

The cyclization of **6e** gave only a minor amount of the required **7e** (the precursor of methylenomycin B), while the major product from the reaction was identified as the β-substituted ethylcyclopentenone **10** [mp 84–85 °C (from CCl_4)], obtained in a ratio of 1:6 **7e**/**10** (71%).[11] The formation of these two products is seen as apparently arising from two types of allyl anion intermediates, **9a** and **9b**. The other possibility, the cyclohexanone **11**, which could result from the cyclization of anion **9c**, was not detected (Scheme II).

A modified approach was then used to prepare compound **7e**. Thus when **7f** or **8f** was treated with 1 equiv of LDA in THF/HMPA (10:1) solution followed by addition of methyl iodide, the desired product **7e** was obtained in excellent yield.[12]

Vacuum pyrolysis of spirocyclopentenones **7a–f** and **10** at 400–450 °C (0.05 mm)[13] afforded the corresponding α-methylenecyclopentenones **12** in nearly quantitative



7a-f, 10 12

yields.[10] The liquid methylenecyclopentenones **12e,f,h** (R^1 = Et, R^2 = H) could be further vacuum distilled if needed. However, this was unnecessary since crude pyrolysates from vacuum pyrolyses display quite satisfactory NMR spectra. They can be kept indefinitely under vacuum or argon at −78 °C but polymerize readily at room temperature, especially in solution. The solid samples **12a–d** could be crystallized from methylene chloride/hexane or ether/hexane mixtures. The crystalline products are quite stable and can be stored without any special precaution.

The pyrolysate from the vacuum pyrolysis of **7g** gave, rather interestingly, an NMR spectrum in which could be observed not only the proton resonances assigned to **12g** [the parent compound in this series: NMR (CCl_4) δ 3.21 (2 H), 5.32 (1 H), 5.88 (1 H), 6.21 (1 H), 7.52 (1 H)] but also another set of signals attributed to the isomer **13** [δ

13

2.82 (2 H), 5.18 (1 H), 5.55 (1 H), 6.31 (1 H), 6.61 (1 H)] in a ratio of 4:1, respectively.[14] No attempt was made to separate these two products due to spontaneous polymerization.

In conclusion, we have described a short and novel method for the general synthesis of α-methylenecyclopentenones which looks like a very attractive process. The retro-Diels–Alder reaction works efficiently under the employed conditions for these fairly small molecules. Thus, the method provides a high-yield synthesis of methylenomycin B (**2** or **12e**, 74% overall yield starting from **5**).

Acknowledgment. We thank The National Research Council (Thailand) for the support.

Registry No. **5**, 13294-86-5; **6a**, 79655-54-2; **6b**, 79655-53-1; **6c**, 79655-55-3; **6d**, 79655-56-4; **6e**, 79667-43-9; **6f**, 79667-42-8; **6g**, 79667-41-7; **7a**, 79655-58-6; **7b**, 79655-57-5; **7c**, 79655-59-7; **7d**, 79655-60-0; **7e**, 79655-63-3; **7f**, 79655-62-2; **7g**, 79655-61-1; **8f**, 79655-67-7; **8g**, 79655-68-8; **10**, 79655-64-4; **12a**, 79655-70-2; **12b**, 79655-69-9; **12c**, 79655-71-3; **12d**, 79655-72-4; **12e**, 52775-77-6; **12f**, 79655-74-6; **12g**, 79655-73-5; **12h**, 80160-98-1; **13**, 80160-99-2.

Supplementary Material Available: Experimental procedure for the synthesis of and characterization data for compounds **7**, **8**, **10**, and **12** (12 pages). Ordering information is given on any current masthead page.

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(8) Prempree, P.; Siwapinyoyos, T.; Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron Lett.* **1980**, 1169.
(9) It was found that the solvent ystem THF/TMEDA (4:1) gave different results from those of THF/HMPA (10:1; cf. ref 8). For example, the product **8** was not detected when the latter solvent system was used.
(10) Characterization data on all compounds in this series are available as supplementary material.
(11) This particular cyclization gave, initially, a mixture of several products (TLC; presumably contaminated by nonisomerized spirocyclopentenones, e.g., **8**). This crude mixture was then further treated with LDA in THF/HMPA (10:1) to allow isomerization and, after protonation, yielded **7e** and **10**.
(12) While **8f** gave only **7e** (93%), **7f** yielded **7e** (91%) together with a detectable amount (4%) of **10**. However, the product ratio from this latter reaction is dependent on the reaction conditions and solvent systems employed (for similar observations see the elegant report by: Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501).
(13) For complete pyrolysis a long heating column (30 in. × 0.5 in. glass column packed with glass chips and wrapped with a heating coil) was used. Numerous reports have appeared on the generation of highly reactive olefins by the retro-Diels–Alder reaction; for the latest review see: Ripoll, J. L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19 (Tetrahedron Report No. 45).
(14) Vacuum pyrolysis of **8g** was also investigated, and it was found that the pyrolysate gave an NMR spectrum very similar to that of **7g**.

On the Reaction of Lithium Diisopropylamide with π-Deficient Heteroaromatics. A Single Electron Transfer Mechanism

Summary: Evidence is presented in support of one-electron transfer as the key step in the reaction of lithium diisopropylamide (LDA) with π-deficient heteroaromatics.

Sir: Since the discovery that pyridine can be coupled with lithium diisopropylamide to afford 2,2′-bipyridine (**1**),[1] this reaction has been utilized in the preparation of various heteroaromatic compounds.[2] Speculation on the mecha-

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(2) Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 1.

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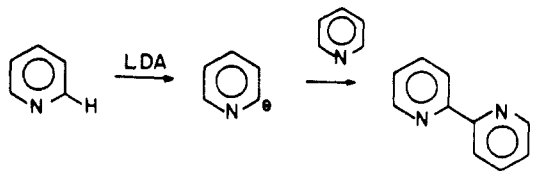

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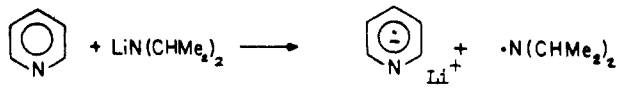
nism of this reaction has been limited to an anionic process involving initial hydrogen abstraction by LDA to generate a carbanion, as the reactive intermediate,[1,3] which undergoes nucleophilic addition to a second equivalent of pyridine. Recently, Ashby and co-workers[4] have shown that LDA is an efficient one-electron donor to molecules which have favorable reduction potentials. We herein extend their findings on one-electron transfer and propose that these heteroaromatic coupling reactions probably occur via a radical–anion intermediate, initiated by one-electron transfer from LDA.

Although a carbanionic mechanism has been invoked for this process, a wide variety of trapping agents have failed to intercept this intermediate,[1] with the possible exception of aldehydes and ketones.[1,3] The calculated order of stability for pyridyl anions is 3- > 4- > 2-,[5] further supporting the unlikelyhood that pyridine with LDA preferentially produces a 2-pyridyl carbanion. In order to investigate the possiblity of radical–anion intermediates being involved, we undertook an ESR study of the reaction of pyridine with LDA.

A 10^{-2} M solution of pyridine in THF with 1 equiv of LDA at −60 °C gave a strong ESR signal characteristic of the diisopropylamino radical,[6] which grew in intensity over several hours and disappeared only slowly when the sample was warmed to room temperature. No signal for the pyridine radical–anion was detected in this sample, its formation only inferred by the appearance of the diisopropylamino radical. However, other workers have shown that the pyridine radical–anion dimerizes instantly in THF, and all previous attempts to observe its ESR signal in this solvent have failed.[7] In later studies HMPA was found to stabilize the pyridine radical anion so that its ESR spectrum was observable.[8] Thus, when equimolar amounts (10^{-2} M) of pyridine and LDA were combined in HMPA at 0 °C, a strong, complex ESR signal was immediately obtained which corresponded to both the pyridine radical–anion (**2**) and the diisopropylamino radical (**3**).[9]



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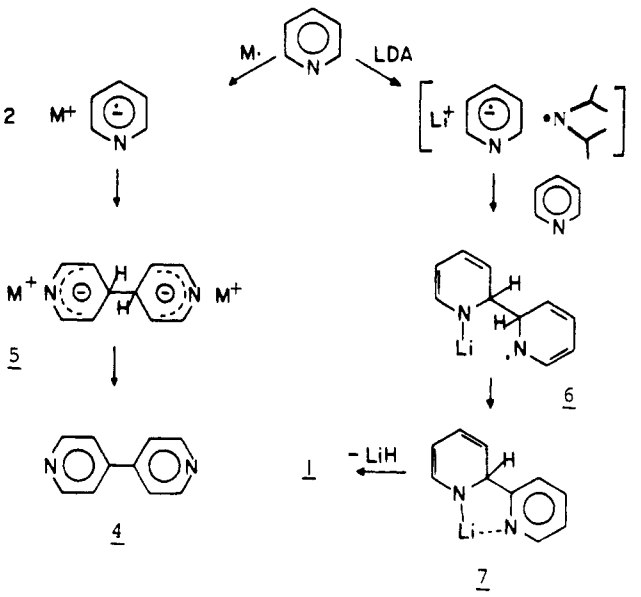
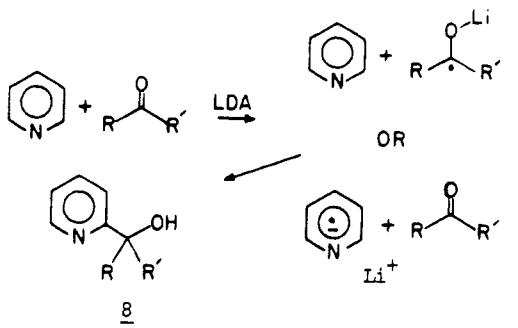
To ascertain which, if any, isomeric dipyridines were produced with HMPA as solvent, we reacted pyridine with LDA in HMPA at 0 °C for 8 h; a subsequent workup afforded 4,4′-bipyridine and 2,4′-bipyridine[10] in yields of

Scheme I



Scheme II



35% and 4%, respectively. No trace of any of 2,2′-bipyridine was detected. The isolation of 4,4′-bipyridine from this reaction leaves little doubt as to the formation of the pyridine radical–anion, since it is well established that the dimerization of pyridine with alkali metals to give 4,4′-bipyridine (**4**) proceeds via a radical–anion intermediate.[8] The reason for the difference in regioselectivity between alkali metal coupling and LDA coupling in THF is yet unresolved; however, a possible explanation is that with alkali metals in HMPA the free radical–anion couples, producing a 4,4′-coupled dianion, **5** (Scheme I), which minimizes cation–cation repulsion. With LDA/THF the solvated radical–anion radical pair can react with a neutral pyridine molecule to give radical **6**,[11,12] that subsequently can lose H· to generate the stabilized anion **7**, which is identical with that derived by an anionic process.

In order to rationalize the successful use of aldehydes and ketones, as trapping agents, in the reaction of LDA with π-deficient heteroaromatics, it can be envisioned as simply a modification of the well-known Emmert reaction,[13] used for the synthesis of heterocyclic alcohols **8**

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(10) 2,4′-Dipyridine is formed through rearrangement of disodium tetrahydrobipyridyl: Cairns, J. F.; Dransfield, P. B.; Imperial Chemical Industries Ltd. U. K. Patent 1 402 195, 1975; *Chem. Abstr.* **1975**, *83*, 164015.
(11) Radical-anion attack on a neutral aromatic moeity has recently been postulated: Collins, C. J.; Hombach, H.-P.; Maxwell, G. E.; Benjamin, B. M.; Mckamey, D. *J. Am. Chem. Soc.* **1981**, *103*, 1213.
(12) An alternate mechanism has been suggested by Professor Cal Y. Meyers in which the tightly bound RARP rearranges via loss of H· to give the 2-pyridyl anion as the reactive intermediate. Experiments to differentiate between the two pathways are currently being attempted.

(Scheme II), in which LDA replaces reducing metals as the electron donor. It is important to note that in many cases one-electron reduction of the (hetero) aromatic moiety may be more facile than the reacting carbonyl compound, providing an alternate mechanistic pathway not previously considered.[14]

A brief review of the literature reveals reactions with other anions which are candidates for the SET mechanism. The reactions of pyridine with Na/NH_3,[10] Na^+-(α-methylstyrene)$_4^-$ Na^+,[15] and alkyl-substituted dithiane anion,[16] of quinoxaline with $NaNH_2$ in *N,N*-dimethylaniline,[17] and of NaOMe with 5-azacinnoline[18] and substituted 1,2,4-triazines[19] all form coupled products which can be envisioned as proceeding through radical-anion intermediates. Studies are currently underway to extend the synthetic utility of this process and to (re)discover hidden anionic one-electron donor systems.

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Registry No. 2, 34516-74-0; 3, 29685-07-2; 4, 553-26-4; pyridine, 110-86-1; lithium diisopropylamide, 4111-54-0; 2,4'-bipyridine, 581-47-5.

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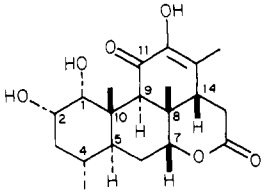
Synthetic Studies on Quassinoids: Total Synthesis of *dl*-Castelanolide

Summary: The quassinoid castelanolide (1) has been synthesized from tetracyclic alcohol 4, thereby confirming the original structural assignment.

Sir: As a result of a detailed examination of *Castela nicholsoni* (Simaroubacaea), a plant known to exhibit antiamebic activity, Geissman and co-workers isolated in the early seventies two new quassinoids, castelanolide (1) and chaparrolide (2).[1] Much attention continues focused on



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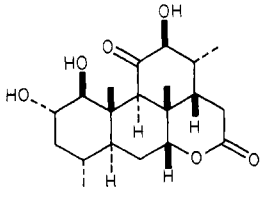

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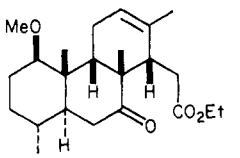
quassinoids[2,3] because of their potent in vivo antineoplastic activity,[4] recently observed antimalarial properties,[5] and their ability to inhibit cell transformation.[6] Despite the vast number of quassinoids which have been fully characterized during the last 20 years,[2] success at total synthesis has been limited to one published account.[7] We record herein the total synthesis of racemic castelanolide which confirms the structural assignment made via classical methods by Geissman over 10 years ago.

The location of the nine chiral centers in castelanolide coupled with its highly oxygenated carbon backbone suggested as a possible starting point the tetracyclic alcohol 4 prepared previously[7] by a four-step sequence from the known Diels-Alder adduct 3.[3k,8] The use of 4 ensures the



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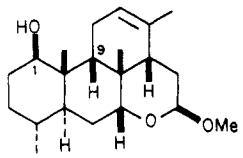

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proper configuration at six [C(4), C(5), C(7), C(8), C(10), and C(14)] of the nine chiral centers. Transformation of 4 into castelanolide requires the following: (a) elaboration of the ring C diosphenol moiety, (b) inversion of configuration at C(9), (c) introduction of the C(1)-C(2) α oriented vicinal diol unit, and (d) unmasking of the δ-lactone. Toward this end, tetracyclic alcohol 4,[7] mp 161-163 °C, was subjected to tetrahydropyranylation (DHP, PPTS,[9] CH_2Cl_2, 25 °C, 2.5 h) followed by hydroboration (B_2H_6, THF, 0 → 25 °C, 3 h; 30% H_2O_2, OH^-, 50 °C, 2 h) of the C(12)-C(13) olefinic bond, giving rise (80% overall) to

(1) Mitchell, R. E.; Stöcklin, W.; Stefanović, M.; Geissman, T. A. *Phytochemistry* **1971**, *10*, 411.

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(3) For synthetic efforts at Quassinoid total synthesis, see: (a) Stojanac, N.; Sood, A.; Stojanac, Z; Valenta, Z. *Can. J. Chem.* **1975**, *53*, 619. (b) Koch, H. J.; Pfenninger, H.; Graf, W. *Helv. Chim. Acta* **1975**, *58*, 1727. (c) Dias, J. R.; Ramachandra, R. *Tetrahedron Lett.* **1976**, 3685. (d) Dias, J. R.; Ramachandra, R. *J. Org. Chem.* **1977**, *42*, 1613. (e) Dias, J. R.; Ramachandra, R. *Synth. Commun.* **1977**, *7*, 293. (f) Dias, J. R.; Ramachandra, R. *J. Org. Chem.* **1977**, *42*, 3584. (g) Snitman, D. L.; Tsai, M.-Y.; Watt., D. S. *Synth. Commun.* **1978**, *8*, 195. (h) Stojanac, N.; Stojanac, Z.; White, P. S.; Valenta, Z. *Can J. Chem.* **1979**, *57*, 3346. (i) Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (j) Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. (k) Grieco, P. A.; Vidari, G.; Ferriño, S.; Haltiwanger, R. C. *Tetrahedron Lett.* **1980**, 1619. (l) Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (m) Okano, M.; Lee, K.-H. *J. Org. Chem.* **1981**, *46*, 1138.
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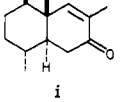
(8) The Diels-Alder adduct 3 was previously prepared[3k] in 40% yield by the reaction of dienophile i with excess diene ii at ambient temper-



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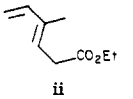

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ature (30 h) in benzene containing 0.25 equiv of aluminum chloride and 0.02 equiv of 4,4'-thiobis(6-*tert*-butyl-3-methylphenol). The yield of this remarkable Diels-Alder reaction has been improved to 64% (based on isolated crystalline material) by substituting ethylaluminum dichloride in place of aluminum chloride and allowing the reaction to proceed over a 72-h period.
(9) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

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