Communications

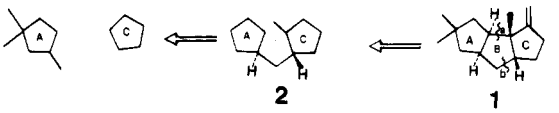
The Nitrone Route to Linearly Fused Tricyclopentanoids. Another Synthesis of Hirsutene

Summary: A novel approach to the linearly fused tricyclopentanoid framework involving an intramolecular nitrone–olefin cycloaddition is described in the context of a hirsutene total synthesis.

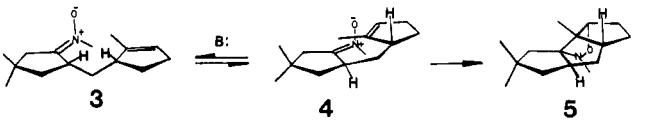
Sir: In recent years synthetic chemists have aggressively developed new methodology for polyquinane total synthesis[1] due, in part, to the aesthetically appealing topologies of this class of compounds, and in some cases, interesting biological activity.[2] We, too, are intrigued and have initially directed our attention to the linearly fused tricyclopentanoid ring system, e.g., the hirsutane class of compounds. The majority of the existing synthetic approaches[3] involve successive annelation of five-membered rings onto a cyclopentane derivative (i.e., A → AB → ABC or B → AB → ABC, etc.). The synthetic routes of Little[3i] and Curran[3p] are noteworthy in that two cyclopentane rings are annelated simultaneously (A → ABC and B → ABC, respectively). The exceptional strategy of Wender[3k] defies simple classification since an arene–olefin was utilized as the starting material instead of the typical cyclopentane derivative (x → y → ABC?).

A conceptually unique and deceptively attractive approach to linearly fused tricyclopentanoids is outlined in Scheme I. In this strategy, two substituted cyclopentanes are joined together to create the central five-membered ring and thus complete the triquinane skeleton (A + C → AC → ABC). A formidable obstacle in this approach is the control of the remote, relative stereochemistry in **2** if one chooses initial formation of bond b (similar stereochemical requirements, although vicinal, are encountered in the bond a option.)[4] This problem can be circumvented

Scheme I

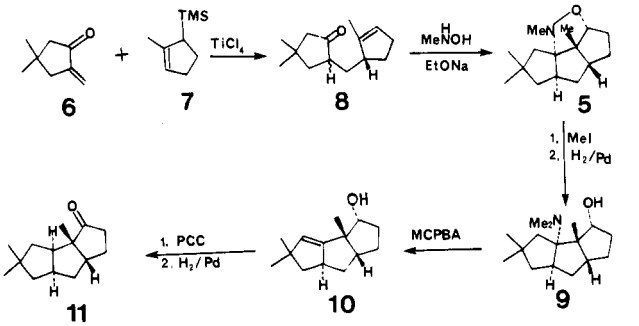


Scheme II



if one employs a reaction for formation of bond a in **2** that discriminates between the anti stereoisomer **2** and the syn isomer and, moreover, induces in situ equilibration of the syn and anti isomers. An appealing candidate reaction is shown in Scheme II. Inspection of molecular models reveals that the intramolecular nitrone–olefin cycloaddition is impossible for the syn isomer **3** but quite feasible for the anti isomer **4**. Under basic conditions, nitrone **3** should epimerize and also give rise to the cycloadduct **5** which possesses the correct relative stereochemistry and functionality useful for completion of the hirsutene (**1**) total synthesis. Herein, we report the realization of this strategy.

The nitrone precursor, ketone **8**, was easily prepared by using a modified Sakurai reaction[6], that is, inverse addition of a mixture of enone **6**[7,8] and $TiCl_4$ to allylsilane **7**[9] in CH_2Cl_2 (71%). As expected, the ^{13}C NMR spectrum of



8 indicated a mixture of stereoisomers (2:1). Separation of these isomers could only be achieved by using HPLC (EtOAc/hexanes, 1:19). Each of the isomers was independently converted to the corresponding *N*-methyl nitrone **3**/**4** (1.1 equiv of MeNHOH·HCl, 3 equiv of NaOEt, EtOH, toluene). After refluxing for 24–36 h, both isomers afforded the same cycloadduct **5**. (When stoichiometric quantities of NaOEt were used, the major isomer led to

(1) For reviews, see: (a) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (b) Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141. (c) Demuth, M.; Schaffner, K. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 820.

(2) For example, inhibitory activity on ($Na^+ + K^+$)-ATPase from tumor cells by coriolin derivatives: Kunimoto, T.; Umezawa, H. *Biochem. Biophys. Acta* **1973**, *318*, 78.

(3) For previous syntheses of hirsutene, see: (a) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Tetrahedron Lett.* **1976**, 195. (b) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1976**, 2795. (c) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1978**, 1991. (d) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1979**, *101*, 6116. (e) Greene, A. E. *Tetrahedron Lett.* **1980**, *21*, 3059. (f) Hudlicky, T.; Kutchan, T.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351. (g) Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020. (h) Mehta, G.; Reddy, A. V. *J. Chem. Soc., Chem. Commun.* **1981**, 756. (i) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744. (j) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Helv. Chim. Acta* **1981**, *64*, 1347. (k) Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1982**, *23*, 3983. (l) Ley, S. V.; Murray, P. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1252. (m) Magnus, P.; Quagliato, D. A. *Organometallics* **1982**, *1*, 1243. (n) Dawson, B. A.; Ghosh, A. K.; Jurlina, J. L.; Stothers, J. B. *J. Chem. Soc., Chem. Commun.* **1983**, 204. (o) Little, R. D.; Higby, R. G.; Moeller, K. D. *J. Org. Chem.* **1983**, *48*, 3139. For syntheses of other hirsutanes (hirsutic acid C and the coriolins), see: Greene, A. E.; Luche, M.-J.; Deprês, J.-P. *J. Am. Chem. Soc.* **1983**, *105*, 2435 and references cited therein. (p) Curran, D. P.; Rakiewicz, D. M. "Abstracts of Papers", 187th National Meeting of the American Chemical Society, St. Louis, 1984, American Chemical Society: Washington, DC, 1984; Abstract 30.

(4) While this work was in progress, a hirsutene synthesis which employs this basic strategy was reported.[3l] Indeed, these stereochemical requirements proved troublesome.

(5) For reviews, see: (a) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 10. (c) Padwa, A. *Ibid.* **1976**, *15*, 123. (d) Black, D. St. C; Crozier, F.; Davis, V. C. *Synthesis* **1975**, 205.

(6) Sakurai, H.; Hosomi, A. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

(7) All new compounds reported herein exhibited satisfactory spectral (IR, NMR), analytical, and/or high-resolution mass spectral characteristics.

(8) Obtained in 50% overall yield from methyl 2-oxo-4,4-dimethylcyclopentanecarboxylate by the following sequence: (1) $HOCH_2CH_2OH$, H^+; (2) LAH; (3) H_3O^+; (4) TsCl, pyridine, DBN.

(9) Obtained by trimethylsilylation of (2-methyl-2-cyclopentenyl)-magnesium chloride (60%).

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intractable material upon continued heating, whereas the minor isomer rapidly cyclized.) Alternatively, the isomeric mixture of ketones **8** can be used directly to provide isoxazolidine **5** in 75% yield.

Completion of the hirsutene total synthesis requires stereospecific reductive deamination. We chose a Cope elimination–hydrogenation sequence to effect this transformation. Thus, methylation (xs MeI) of isoxazolidine **5** and subsequent N–O scission (H_2/Pd) gave amino alcohol **9** (89% overall yield). Cope elimination of the corresponding amine oxide (MCPBA, CH_2Cl_2, aqueous $NaHCO_3$, 50 °C, 48 h; 90%) gave only **10** and none of the regioisomeric elimination product with the double bond endocyclic to both rings (>98:2 by ^{13}C NMR spectral analysis). Although the factor(s) responsible for this selectivity are not evident, it should be noted that the olefin moiety in **10** offers access to the C-11 α-hydroxyl present in coriolin. The synthesis was concluded by oxidation of alcohol **10** followed by stereospecific hydrogenation to furnish the known ketone **11** (65%) which was identical in all respects (IR, ^1H 360-MHz NMR, ^{13}C NMR, mp) with an authentic sample and spectra kindly furnished by Professors Hudlicky and Curran. Ketone **11** has been previously converted to *dl*-hirsutene (1) by reaction with methylenetriphenylphosphorane.[3a]

In summation, we have reported a new strategy for the stereospecific and expedient assemblage of the linearly fused tricyclopentanoid framework. The versatility of this methodology remains to be documented and consequently we are investigating its further application.

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Directed Ortho Metalation Induced Epoxy Cyclialkylation. Regiospecific 5-Exo-Tet and 6-Exo-Tet Routes to Benzofurans and Benzopyrans

Summary: Metalation of epoxybenzamides **7a–d**, **11**, **13**, **15** occurs by regiospecific 5-exo-tet and 6-exo-tet ring-closure modes and leads to benzofuran and benzopyran derivatives **8a–d**, **12**, **14**, **16**.

Sir: Strategies for carbon–carbon bond-forming annelation to an aromatic ring are generally based on Friedel–Crafts methodology[1] and are therefore dictated by the rules of classical aromatic electrophilic substitution. The anionic equivalent of the Friedel–Crafts and related reactions (Scheme I, **1a,b** → **2a,b** → **3a,b**) discovered by Parham[2] constitutes a new concept with broad, as yet unexploited, synthetic potential[3] which, however, is dependent on the metal–halogen exchange process and thus on the availability of ortho-bromo substituted reactants. Likewise dependent and synthetically underdeveloped is the anionic epoxy cyclialkylation variant[4,5] **1c** → **2c** → **3c** recently disclosed by Bradsher[6] and by Durst.[7] Herein we report on a new anionic heteroring epoxy cyclialkylation **4** → **5** → **6** whose regiospecificity originates solely with the powerful directed ortho metalation character of the tertiary amide function.[8] This method, following 5-exo-tet and 6-exo-tet modes,[9] provides a useful and potentially general protocol for the construction of unusually substituted benzofuran and benzopyran systems.

Scheme I

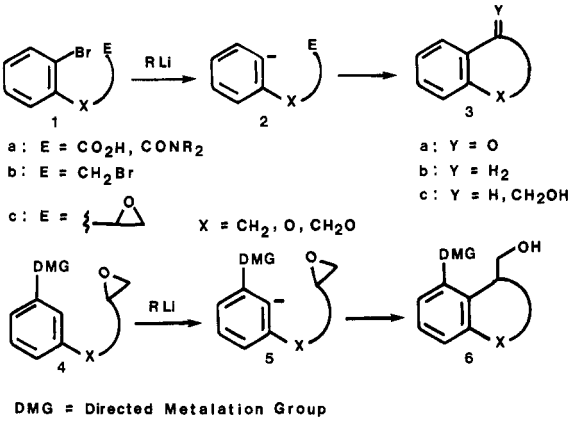

Table I. Directed Ortho Metalation Induced Epoxy Cyclialkylations

substrate	product	yield,[a] %	mp, °C
7a	**8a**	67	*b*
7b	**8b**	60	*b*
7c	**8c**	64	133–134[c]
7d	**8d**	68	90–91[c]
11	**12**	53	115–116[c]
13	**14**	65	103–105[c]
15	**16**	32	*b*
17	**18**	38	*b,d*

[a] Yields correspond to purified (silica gel chromatography (hexane–EtOAc) or crystallization) materials. [b] Oil, purified by chromatography, homogeneous by TLC in several solvent systems. [c] Recrystallized from CH_2Cl_2–hexane. [d] 3 equiv of *sec*-BuLi/TMEDA were required to effect cylization.

Standard metalation (1.5 equiv of *sec*-BuLi/TMEDA/THF/–78 °C)[8] of **7a**[10,11] followed by warming to am-

(1) Olah, G. A. Ed. "Friedel–Crafts and Related Reactions"; Interscience; New York, 1963; Vol. I–IV.
(2) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.
(3) This potential is in the early stages of exploitation: Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.
(4) The corresponding epoxy cyclialkylation of α-stabilized carbanions is a well-established synthetic tactic: Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323. Decesare, J. M.; Corbel, B.; Durst, T.; Blout, J. F. *Can. J. Chem.* **1981**, *59*, 1415 and references cited therein.
(5) The Lewis acid promoted epoxy cyclialkylation is receiving initial attention: (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983**, *48*, 2449.
(6) Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1978**, *43*, 3800.
(7) Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* **1980**, *45*, 922.
(8) Review: Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.
(9) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(10) Epoxy amides **7a–e**, **11**, **13**, **15** and **17** were prepared in 70–80% yields from *N,N*-diethyl-3-methoxybenzamide as follows: (1) BBr_3/CH_2Cl_2/–78 °C → RT/14 h; (2) NaH/$R^3R^2C{=}C(R^1)CH_2Br$/DMF/0 °C → RT/6 h; (3) MCPBA/CH_2Cl_2/RT/24–48 h and purified by column chromatography (silica gel, hexane–Et_2O) before use.

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