Sequential "Double-Michael" Additions of Dienolates to Fulvene: Rapid Access to the Tricyclo[5.3.0.n^{2,5}]alkane Systems

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Summary: A highly efficient and stereoselective approach to the tricyclo-[5.3.0.n^{2,5}]alkan-4-one system has been achieved via the intermolecular double Michael reaction of lithium dienolates to fulvene. Copyright © 1996 Elsevier Science Ltd

The synthesis of the hydroazulenic sesquiterpenes has received a great deal of attention over the years. However, general methodologies for the synthesis of the hydroazulene skeleton are scarce and issues of stereochemical control about this flexible nucleus have remained largely unsolved.[1]

In conjunction with our continuing interest in the reactions of fulvenes,[2] we have developed a fundamentally new approach to the construction of the tricyclic[5.3.0.n^{2,5}]alkane ring systems, namely the skeletons of isobarbatene (1)[3] and rotundenol (2).[4] Isobarbatene (1) is a novel crystalline tricyclic compound which was isolated in near quantitative yield upon trifluoroacetic acid treatment of the liverwort sesquiterpenes β-bazzanene, α and β-barbatene, gymnotmitrol and (+)-α-chamigrene (Scheme 1).[5] Rotundenol (2) was isolated from the hydrocarbon fraction of *C.scariosus* (Indian origin) and *C.rotundus* (Chinese origin).[6,7]

Scheme 1

β-bazzanene

α-barbatene R = H
β-barbatene R = OH

(+)-α-chamigrene

Isobarbatene   1

Rotundenol   2
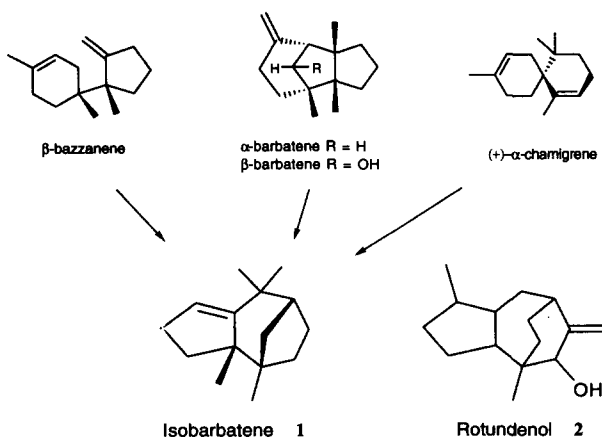
Both **1** and **2** share a related hydrocarbon skeleton. A logical and facile way to assemble the framework of **1** would be through an α double cyclization of 6,6-dimethylfulvene and the enolate of cyclopentenone (Scheme 2).[8] It has been reported that 6,6-dimethylfulvene acts like an electron deficient olefin with reactivity similar to an α,β unsaturated carbonyl.[9] Therefore, it seemed likely that a dienolate anion, formed by the α-deprotonation of an enone could add in a Michael-like fashion to fulvene and form an anionic intermediate which would then cyclize through an intramolecular Michael reaction, affording the tricyclic ketone intermediate upon protonation.
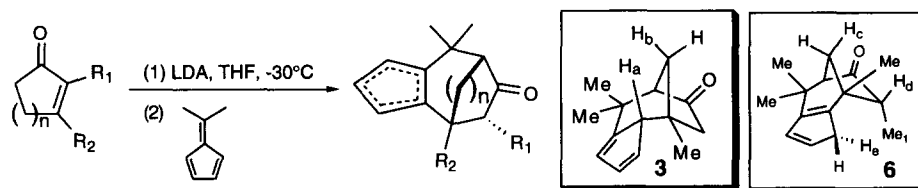
Scheme 2
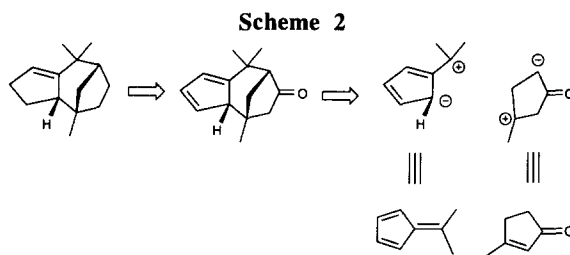
Addition of a THF solution of 6,6-dimethylfulvene to a mixture of methylcyclopentenone and LDA in THF at -30 °C provided the tricyclic ketone **3** in 96% yield as the only detectable diastereomer (entry 1, Table 1). The structure of **3** was assigned based on ^{1}H, ^{13}C NMR, COSY, DEPT, HETCOR, COLOC and mass spectral data.[10] The first step in this reaction is presumably the α'-alkylation of the C-6 of fulvene by the methylcyclopentenone enolate, followed by intramolecular cyclization to generate **3**.

The relative configuration of the fused tricyclic system **3** was determined from a 2D NOESY experiment. The spectrum showed a key correlation between H_a (broad singlet at 2.96 ppm) and H_b (double doublet at 2.25 ppm), which supports the structure depicted in Table 1. A series of homologous enones were subjected to the dienolate addition to give the cyclic ketones **4-10** (Table 1). The reaction of some of the enones with fulvene resulted in the formation of the unsaturated tricycloalkenone isomers **5** to **10** (entries 3-8, Table 1). The isomerization of the cyclopentadiene double bonds maybe attributed to a facile 1,5-H shift which leads to the thermodynamically more stable skeleton.[10] In fact, a solution of ketone **3** in refluxing benzene (1h) gives rise to all three double bond positional isomers. As illustrated by the entries of Table 1, this new sequential cycloaddition allows a rapid and efficient entry into the tricyclic [5.3.0.n^{2,5}] alkane ring systems.

Typical experimental procedure: To a solution of diisopropylamine (232 mg, 2.3 mmol) in dry THF (25 mL) was added n-BuLi (1.6M in hexane, 1.4 mL, 2.2 mmol) and the solution was stirred at -78°C for 20 min. A solution of 3-methyl-2-cyclopenten-1-one (200 mg, 2.1 mmol) in THF (25 mL) was added and the mixture was stirred at -78°C for 30 min. A solution of 6,6-dimethylfulvene (200 mg, 1.8 mmol) in THF (10 mL) was added to the enolate solution at -78°C, and the resulting mixture was warmed to -35°C and stirred for 90 min. The reaction was quenched with H_2O (1 mL), diluted with EtOAc, washed with brine, dried over Na_2SO_4, concentrated *in vacuo* and the residue was purified by flash column chromatography with 2% EtOAc-hexane (R_f = 0.45 in 5% EtOAc-hexane) to give ketone **3** as a colorless oil (349 mg, 96% yield). IR (neat): 2968, 2880, 1750, 1467, 1261, 1183, 1090 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 6.44 (ddd, J = 5.4, 1.8, 1.8 Hz, 1 H), 6.25 (ddd, J = 5.4, 1.4, 1.4 Hz, 1 H), 5.97 (ddd, J = 1.9, 1.2, 1.2 Hz, 1 H), 2.96 (br. s, 1 H), 2.25 (dd, J = 12.7, 3.6 Hz, 1 H), 2.04 (d, J = 5.1 Hz, 1 H), 1.68 (dd, J = 12.7, 5.1

Hz, 1 H), 1.36 (s, 3 H), 1.36-1.19 (m, 2 H), 1.22 (s, 3 H), 1.19 (s, 3 H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 218.75 (C), 154.53 (C), 133.90 (CH), 132.63 (CH), 123.95 (CH), 59.97 (CH), 59.59 (CH), 43.88 (CH$_2$), 41.97 (C), 39.85 (CH$_2$), 37.62 (C), 28.92 (CH$_3$), 26.01 (CH$_3$), 24.76 (CH$_3$); MS (m/z, relative intensity): 202 (M$^+$, 45), 187 (21), 159 (21), 153 (23), 145 (100), 131 (22), 107 (24), 91 (21), 89 (24), 83 (25), 77 (56); exact mass calculated for C$_{14}$H$_{18}$O (M$^+$): 202.1358; found 202.1355.

Table 1. Sequential "Double-Michael" Additions of Dienolates to fulvenes

Entry	Enone	Product	Temperature	Yields(%)[a]
1		3	-78°C→ -35°C	96
2		4	-78°C→ -30°C	75
3		5	-78°C→ -30°C	70[b]
4		6	-78°C→ -35°C	94[b][c]
5		7	-78°C→ -20°C	78
6		8	-78°C→ -30°C	78
7		9	-78°C→ 25°C	40
8		10	-78°C→ 25°C	52

(a) Isolated yield based on starting fulvene.
(b) The formation of the endo C4-methyl followed from protonation of the enolate on the less hindered exo-face of the molecule. Epimerization of the endo methyl group to exo occurred at the basic condition (KOH/MeOH, 25°C).
(c) The relative configuration of 6 was determined from a 2 D NOESY experiment. The spectrum which showed key correlations between H$_c$ and H$_d$, H$_e$ and Me$_1$ supports the structure depicted in this table.

In summary, the double-Michael addition sequence outlined in this paper provides a remarkably efficient route to the tricyclo[5.3.0.n^{2,5}]alkane ring systems. The reaction is particularly attractive in the case of the cyclopentenones as two bonds and three stereocenters are formed in one step with very high stereoselectivity. An extension of this work to the total synthesis of hydroazulenic sesquiterpenes is in progress and the results of these investigations will be reported in due course.

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References and Notes:

1   For a recent review of the synthesis of hydroazulenic sesquiterpenes, see: (a) Ho, T. L. *Carbocyclic Construction in Terpenes Synthesis*, VCH: New York, **1988**. (b) Vandewalle, M.; Clercq, P. D. *Tetrahedron* **1985**, *41*, 1767-1831. (c) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C. in *The Total Synthesis of Natural Products*; ApSimon, J. W., Ed.; Wiley: New York, **1983**, Vol 5, 333-384.

2   For previous papers in this series, see: (b) Hong, B.-C.; Sun, S.-S. *Tetrahedron Lett.* **1996**, *37*, 659-662. (b) Hong, B.-C.; Sun, S.-S. *J. Chem. Soc. Chem. Commun.* **1996**, 937-938.

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5   Due to the ease and high yield of this chemical transformation, it had been expected since 1978 that isobarbartene should also be a natural constituent of sesquiterpene-rich essential oils. Recently, it was isolated for the first time from the roots of the higher plant *Meum athamanticum* (L.) Jacq. See: Koenig, W.; Rieck, A.; Saritas, Y.; Hardt, I. H.; Kubeczka, K.-H. *Phytochemistry* **1996**, *42*, 461-464.

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7   The *Cyperus rotundus* shows herbicidal activity and inhibits prostaglandin biosynthesis. See:
    (a) Harrington, P. M.; Singh, B. K.; Szamosi, I. T.; Birk, J. H. *J. Agric. Food Chem.* **1995**, *43*, 804-808. (b) Sankawa, U. *Igaku no Ayumi* **1983**, *126*, 867-874.

8   The sequential double-Michael addition of a dienolate to C_{60} has been reported in the synthesis of sterically crowded fullerene derivatives with potential anti-HIV-1 activity. See: Ganapathi, P. S.; Friedman, S. H.; Kenyon, G. L.; Rubin, Y. *J. Org. Chem.* **1995**, *60*, 2954-2955.

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10 All new compounds were characterized by full spectroscopic (^{1}H, ^{13}C NMR, COSY, DEPT, HETCOR, NOESY, COLOC, IR, MS, and HRMS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.