Ingenane Synthesis. Construction of the ABC Framework

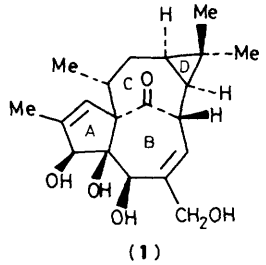
Goverdhan Mehta* and Ved Prakash Pathak

School of Chemistry, University of Hyderabad, Hyderabad 500 134, India

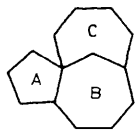
A convenient route to the tricyclo[7.4.1.$0^{1,5}$]tetradecane ring system present in the complex ingenane diterpenes, starting from 2-methoxycarbonylcycloheptanone, is outlined.

The diterpenoid ingenol (**1**)[1] and its esters have earned considerable notoriety as the most common irritant present in the Euphorbia genus with their tumour-promoting biological activity.[2] However, to the synthetic chemist the unique tetracyclic framework of ingenanes, represented here by ingenol (**1**), with dense oxygen functionalisation and stereochemical intricacies, holds special appeal. While the synthesis of (**1**) remains a distant goal, recent studies,[3] notably by Paquette,[3a] have focussed on the creation of the functionalised tricarbocyclic skeleton (**2**) comprising the ABC rings of ingenanes. Indeed, access to ring system (**2**) has been very limited.[3a,b] We report an exceptionally simple synthesis of a functionalised tricyclo[7.4.1.$0^{1,5}$]tetradecane derivative (**10**) from 2-methoxycarbonylcycloheptanone (**3**), which lays the basis for further efforts towards (**1**).

Alkylation of the anion derived from the readily available (**3**)[4] with 4-bromobutyraldehyde dimethyl acetal gave (**4**), which was converted into the trimethylsilyl enol ether (**5**). The titanium(IV)-catalysed intramolecular variant of the Mukaiyama reaction[5] with (**5**) proceeded smoothly to give an approximately 1 : 1 mixture of the bicyclo[4.4.1]undecane-based methyl ethers (**6a,b**). The directed aldol strategy proved to be distinctly superior to the conventional intramolecular alkylation methodology, which is complicated by competing *O*-cyclisation, for creating these large bridged systems.[6] Although the two epimeric methoxy-compounds (**6a, b**) could be separated and characterised, it was not necessary to do so for subsequent steps. Trimethylsilyl iodide[7] efficiently cleaved (**6a, b**) and the resulting hydroxy-compound was oxidised with $PyHCrO_3Cl$ to the bicyclic 1,3-dione (**7**),† m.p. 57 °C.

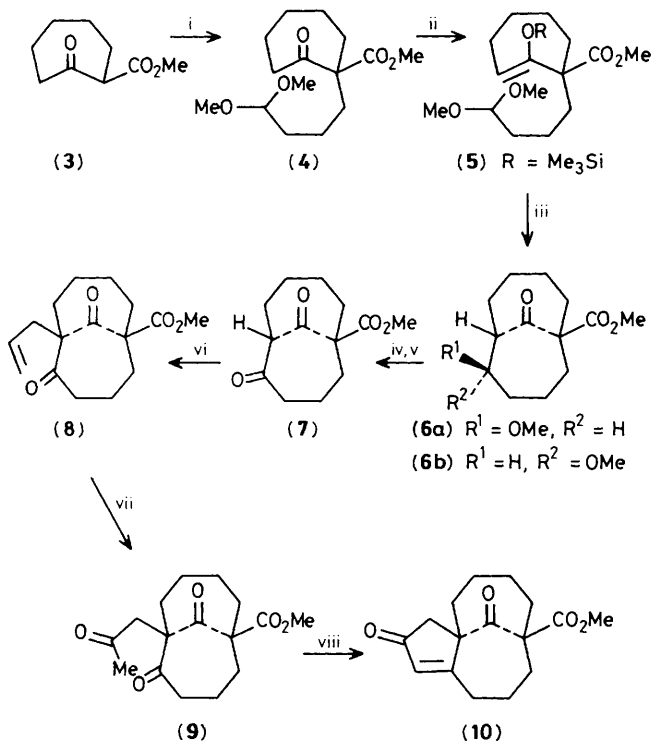


(**1**)



(**2**)

† All new compounds were characterised on the basis of their spectroscopic and analytical data. Selected spectroscopic values for some key compounds are: (**7**): ^{1}H n.m.r. ($CDCl_3$, 100 MHz): δ 3.72 (3H, s), 3.48 (1H, m), 1.4—2.56 (14H, m); ^{13}C-n.m.r. ($CDCl_3$, 25 MHz): δ 210.1, 207.2, 173.3, 67.2, 63.6, 53.3, 43.2, 35.8, 29.6, 26.1, 25.1(2C), 21.1. (**8**): ^{1}H n.m.r. ($CDCl_3$, 100 MHz): δ 5.48 (1H, m), 4.90 (2H, m), 3.64 (3H, s), 2.38 (2H, d, *J* 8 Hz), 1.4—2.28 (14H, m); ^{13}C n.m.r. ($CDCl_3$, 25 MHz): δ 210.2, 210.1, 173.5, 132.7, 119.3, 68.5, 64.4, 52.3, 42.2, 41.6, 35.5, 32.9, 29.9, 25, 24.8, 21.6. (**9**): ^{1}H n.m.r. ($CDCl_3$, 100 MHz): δ 3.76 (3H, s), 3.07 (1H, d, *J* 16Hz), 2.62 (1H, d, *J* 16Hz), 2.22 (s, 3H), 1.44—2.12 (14H, m); ^{13}C-n.m.r. ($CDCl_3$, 25 MHz): δ 212.6, 208.3, 206.3, 172.9, 67.5, 63.4, 52.6, 52.4, 42.7, 35.6, 34.4, 29.9, 29.3, 25.0, 23.9, 21.6.



Scheme 1. *Reagents:* i, NaH, RBr, dimethylformamide (DMF), 58%; ii, Bu^{n}Li, hexamethyldisilazide (HMDS), tetrahydrofuran (THF), Me_3SiCl, −78 °C; then iii, $TiCl_4$, CH_2Cl_2, −78 °C, 66% for two steps; iv, Me_3SiCl, NaI, MeCN, 92%; v, $PyHCrO_3Cl$, 3 Å molecular sieve, 93%; vi, Bu^{n}Li, HMDS, hexamethylphosphoramide (HMPA), THF, −78 °C, then CH_2=CH–CH_2Br, −78 °C—room temp., 70%; vii, $PdCl_2$, Cu_2Cl_2, DMF–H_2O, O_2, 83%; viii, NaH, THF, 71%.

Regioselective allylation of the dione (**7**) was achieved at the desired bridgehead position to give (**8**),† m.p. 79 °C. Tsuji oxidation[8] of (**8**) generated the required acetonyl side-chain and the resulting triketone (**9**),† m.p. 91 °C, was cyclised to the tricyclic enone (**10**), m.p. 111 °C, ^{1}H n.m.r.: δ 5.81 (1H, d, *J* 1.5 Hz); ^{13}C n.m.r.: δ 207.1(s, 2C). 178.7(s), 174.1(s), 130.8 (d), 66.5(s), 64.9(s), 52.3, 47.5, 35.3, 35.1, 31.4, 29.5, 25.6, 25.2, 23.5. The sequence depicted in Scheme 1 offers a useful and practical solution for creating diverse polycyclic bridged systems.

We thank U.G.C. for a Special Assistance Programme in Organic Chemistry and COSIST support for Organic Synthesis.

Received, 4th February 1987; Com. 147

References

1 K. Zechmeister, F. Brandl, W. Hoppe, E. Hecker, H. J. Opferkuch, and W. Adolf, *Tetrahedron Lett.*, 1970, 4075.
2 F. J. Evans and S. E. Taylor in 'Progress in the Chemistry of Organic Natural Products,' Vol. 44, Springer, Vienna & New York, 1983, pp. 1—90.
3 (a) L. A. Paquette, T. J. Nitz, R. J. Ross, and J. P. Springer, *J. Am. Chem. Soc.*, 1984, **106**, 1446; (b) R. L. Funk and G. L. Bolton, *ibid.*, 1986, **108**, 4655; (c) See also P. A. Wender, C. L. Hilleman, and M. J. Szymonifka, *Tetrahedron Lett.*, 1980, 2205.
4 S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, 1963, **19**, 1625; R. W. Carling and A. B. Holmes, *J. Chem. Soc., Chem. Commun.*, 1986, 565.
5 T. Mukaiyama, *Org. React.*, 1982, **28**, 238.
6 I. J. Borowitz and N. Suciu, *J. Org. Chem.*, 1973, **38**, 1061; I. J. Borowitz, G. J. Williams, L. Gross, H. Beller, D. Kurland, N. Suciu, V. Bandurco, and R. D. G. Rigby, *ibid.*, 1972, **37**, 581.
7 G. A. Olah, S. C. Narang, B. G. B. Gupta, and R. Malhotra, *J. Org. Chem.*, 1979, **44**, 1247.
8 J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, 1976, 2975.