Pergamon

Tetrahedron Letters 40 (1999) 4877–4880

TETRAHEDRON
LETTERS

A Stereoselective Total Synthesis of the Novel Sesquiterpene Kelsoene

Goverdhan Mehta,* K. Srinivas

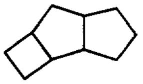
Department of Organic Chemistry, Indian Institute of Science,
Bangalore 560 012, India

Received 24 March 1999; accepted 6 May 1999

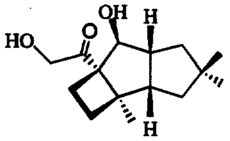
Abstract: Employing commercially available 1,5-cyclooctadiene **5** as the starting material, the first total synthesis of the tricyclic sesquiterpene hydrocarbon kelsoene **3** has been accomplished, which also reaffirms its assigned structure. The basic strategy delineated here for the construction of the tricyclo[6.2.0.0^{2,6}]decane framework is eminently suitable for the synthesis of other members of this class. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: Terpenes; Cyclobutene; Homologation; Wittig reaction

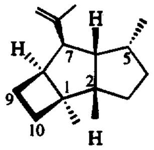
The tricyclo[6.2.0.0^{2,6}]decane framework **1**, composed of 4-5-5 linearly fused carbocyclic rings, has recently been encountered among many terpenic natural products of diverse origin. Some of the notable examples are sulcatine G **2**[1] from a *Basidiomycetes* fungi, kelsoene **3**[2] from the tropical marine sponge *Cymbastela hooperi*[2a] as well as from the liverwort *Ptychanthus straitus*[2b] and poduran **4**[3] from the springtail *Podura aquatica*. Although, the core structure in all these terpenoids is the *cis, anti, cis*-fused tricyclic frame **1**, they deviate markedly in the disposition of alkyl substitution pattern and originate through different biosynthetic pathways.



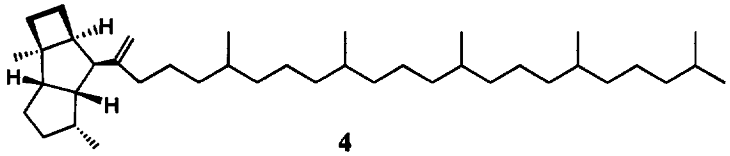
1



2

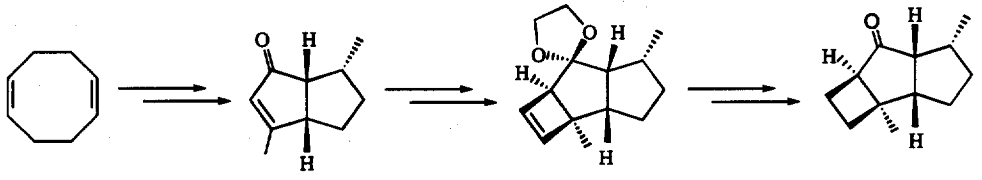


3



4

PII: S0040-4039(99)00901-6



5 6 7 8

Scheme 1

The sesquiterpene kelsoene **3** and the tetraterpene poduran **4**, sharing an identical carbocyclic skeleton with six contiguous stereogenic centres, were first reported[2,3] in 1997 and their structures were determined on the basis of incisive ^{1}H-^{1}H and ^{1}H-^{13}C shift correlation NMR spectroscopy. Both, **3** and **4** drew our attention as attractive synthetic targets and we reasoned that their synthesis would also constitute reaffirmation of their assigned structures. In this context, we have recently outlined a synthesis of the tricarbocyclic core **8**, a projected advanced intermediate enroute to **3** and **4**, from readily available 1,5-cyclooctadiene **5** through the intermediacy of diquinane enone **6** and the tricyclic ketal **7**, Scheme 1.[4,5] Further evolution towards the natural products **3** and **4** required the appendage of an appropriate side chain at C_7 in **8** utilizing the carbonyl handle. However, the carbonyl group in **8** proved to be completely refractory towards homologation manouvres, reflecting the prevailing steric environment around it. This could be readily gleaned through the AM1 minimized structure depicted in Fig. 1a, which showed that while the top-face of the carbonyl group is blocked by the two methyl substituents, the bottom-face is hindered by the presence of the C_9-C_{10} *endo*-hydrogens of the fused cyclobutane ring. Clearly, restoring the C_7-carbonyl reactivity in **8** required the lifting of the steric barrier to one of its faces. Since the steric contribution of the two methyl groups in **8** was not amenable to redress, the option of removing the C_9-C_{10} *endo*-hydrogens to create a reagent approach "window" was considered. A suitable candidate in this context appeared to be the cyclobutene compound **9**. Indeed, its AM1 minimized structure (Fig. 1b) revealed steric decongestion of the bottom-face of the carbonyl and an approach "window' was discernible. The reactivity of **9** has now fully vindicated this surmise and paved the way for the first synthesis of kelsoene **3**, which forms the subject matter of this communication.

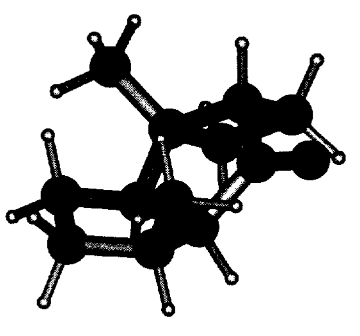


Fig. 1a. AM1 minimized structure of **8**

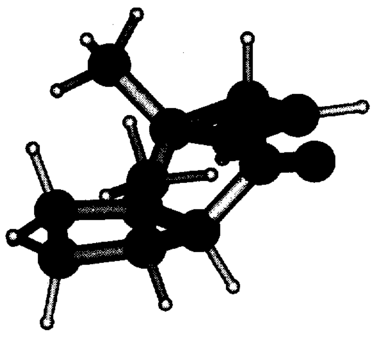
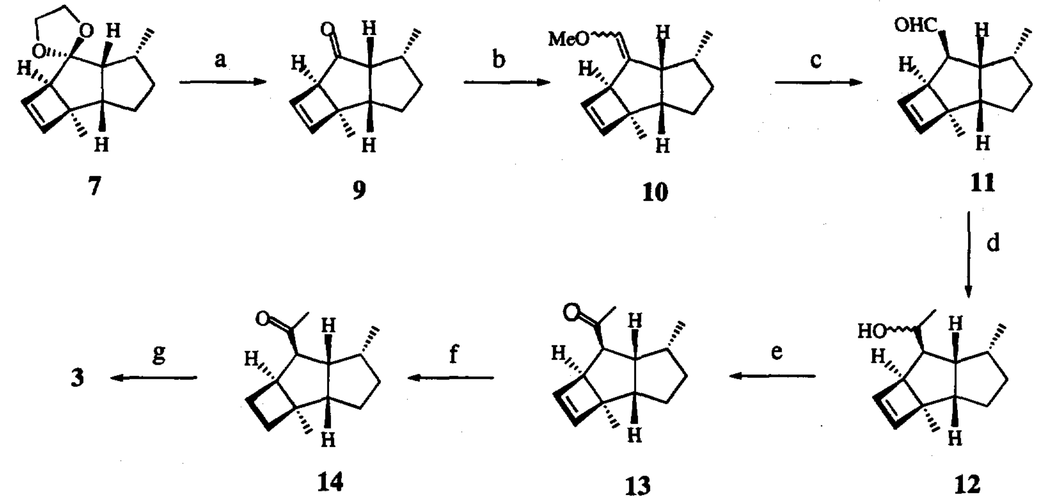


Fig. 1b. AM1 minimized structure of **9**

The tricyclic ketal **7**, previously reported by us,[5] on carefully controlled deprotection yielded **9**, which readily underwent one carbon homologation through Wittig reaction with methoxymethylphosphorane to give **10**.[6] Acid hydrolysis of **10** furnished the C_{13}- aldehyde **11**[6] as a single diastereomer. Addition of methyl lithium (**11**→ **12**) and PCC oxidation led to the C_{14}- methyl



Scheme 2

***Reagents*:** (a) Amberlyst -15, Me_2CO, 85%; (b) $MeOCH_2PPh_3^+Cl^-$, $Na^{+-}O^tAm$, Et_2O, 80%; (c) 35% $HClO_4$, Et_2O, 90%; (d) MeLi, Et_2O, 97%; (e) PCC, DCM, 90%; (f) H_2, 10% Pd/C, EtOAc, 98%, (g) $MePPh_3^+I^-$, $K^{+-}O^tBu$, Et_2O, 80%.

ketone **13**, which was readily hydrogenated to the penultimate precursor **14**[6] of the natural product, Scheme 2. At this stage, it was considered essential to secure independently the stereochemical integrity of **14** at C_7 and therefore a detailed NMR analysis based on ^1H-^1H COSY and NOESY was done and the results are shown in Fig.2.

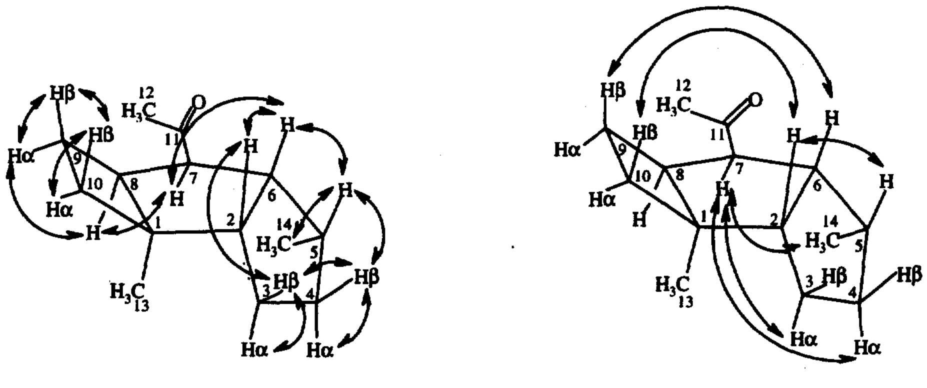


Fig 2 Connectivities using ^1H-^1H COSY

Key NOE's

Thus, the C_7 stereochemistry in **14** corresponding to the natural products **3** and **4** was firmly established. Finally, methylenation of **14** with the ylide derived from methyltriphenylphosphonium iodide delivered the hydrocarbon **3**, which was found to be identical with the natural product kelsoene **3** through the comparison of ^{1}H(300 MHz) and ^{13}C(75 MHz) NMR spectral data.[2,6]

In short, we have accomplished a total synthesis of the tricyclic natural product kelsoene **3**, with good stereochemical control. The simple and flexible strategy employed here can be readily adapted towards the synthesis of other tricyclo[6.2.0.0^{2,6}]decane based natural products through tactical modifications. Efforts along these lines are currently underway.

Acknowledgement: One of us (KS) thanks UGC for the award of a Research Fellowship.

References and Notes:

[1] Anon, A; Nosing, G; Vain de pave, O. *J. Chem. Soc., Perkin Trans 1.* **1993**, 2723.

[2] (a) Konig, G. M; Wright, A. D. *J. Org. Chem.* **1997**, 62, 3837. (b) Nabeta, K.; Yamamoto, K.; Hashimoto, M.; Koshino, H.; Funatsuki, K.; Katoh, K. *Chem. Commun.* **1998**, 1485.

[3] Schulz, S.; Messer, C.; Dettner, K. *Tetrahedron Lett.* **1997**, 38, 2077.

[4] Kelsoene **3** and other tricyclo[6.2.0.0^{2,6}]decane based natural products can be regarded as diquinane derivatives. Synthesis of this class of terpenes has not been accomplished so far. For a recent review on the synthesis of polyquinane natural products, see, Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, 97, 671.

[5] Mehta, G.; Srinivas, K. *Synlett.* **1999**, 0000.

[6] All new compounds reported here were duly characterised on the basis of spectral (IR, ^{1}H and ^{13}C NMR) and analytical data. Selected spectral data: **9**: IR (neat) ν_{max} 3020, 2940, 1720 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (d, J=2.4Hz, 1H), 6.07 (d, J=2.7Hz, 1H), 3.18 (dd as t, J_1=8.1Hz, J_2=7.8Hz, 1H), 2.90 (s, 1H), 2.53 (q, J=8.1Hz, 1H), 2.37-2.24 (m, 1H), 1.81-1.64 (m, 2H), 1.62-1.49 (m, 1H), 1.34-1.24 (m, 1H), 1.32 (s, 3H), 1.13 (d, J=7.2Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 218.4, 149.8, 133.9, 62.6, 55.3, 51.7, 46.0, 37.2, 34.7, 27.3, 19.0, 16.4; EIMS (75 eV) m/z. 176 (M^+); **11:** IR (neat) ν_{max} 3020, 2940, 2700, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.71 (d, J=3.6Hz, 1H), 6.11 (d, J=2.7Hz, 1H), 5.98 (d, J=2.7Hz, 1H), 3.06-3.00 (m, 2H), 2.58 (ddd, J_1=10.5Hz, J_2=7.1Hz, J_3=3.9Hz, 1H), 2.37-2.24 (m, 2H), 1.92-1.81 (m, 1H), 1.68-1.39 (series of m, 3H), 1.24 (s, 3H), 0.87 (d, J=6.9Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 205.4, 145.8, 131.9, 58.7, 56.3, 51.9, 50.6, 49.3, 35.8, 32.7, 25.2, 19.0, 17.5; EIMS (75 eV) m/z 192 (M^++2); **13:** IR (neat) $\nu_{max.}$ 3040, 2960, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.10 (d, J=2.1Hz, 1H), 5.75 (d, J=2.7Hz, 1H), 3.06-3.00 (m, 2H), 2.75 (dd, J_1=10.7Hz, J_2=7.4Hz, 1H), 2.27-2.18 (m, 2H), 2.17 (s, 3H), 1.88-1.79 (m, 1H), 1.65-1.54 (m, 1H), 1.52-1.42 (m, 1H), 1.41-1.27 (m, 1H), 1.24 (s, 3H), 0.81 (d, J=6.9Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 208.5, 145.8, 131.9, 57.6, 56.5, 51.8, 50.1, 48.7, 35.4, 32.9, 30.1, 25.4, 19.3, 17.3; EIMS (75 eV) m/z 204 (M^+); **14:** IR (neat) ν_{max} 2940, 2860, 1700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.26 (ddd, J_1=10.9Hz, J_2=J_3=6.4Hz, 1H), 2.93 (dd, J_1=10.6Hz, J_2=8.2Hz, 1H), 2.66-2.63 (m, 1H), 2.30-2.24 (m, 1H), 2.15-2.10 (m, 1H), 2.06 (s, 3H), 1.96-1.84 (m, 1H), 1.82-1.77 (m, 2H), 1.75-1.70 (m, 1H), 1.58-1.52 (m, 1H), 1.46-1.39 (m, 1H), 1.38-1.31 (m, 1H), 1.30-1.23 (m, 1H), 1.20 (s, 3H), 0.84 (d, J=6.9Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 208.6, 56.7, 55.2, 49.8, 47.6, .47.0, 35.8, 32.9, 32.3, 30.1, 26.0, 23.2, 17.5, 15.3; EIMS (75 eV) m/z 206 (M^+); **3:** IR (neat) ν_{max} 3080, 2960, 2860, 1640, 1450, 1370, 880 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.87 (br s, 1H), 4.80 (br s, 1H), 2.86 (ddd, J_1=10.3Hz, J_2=6.7, Hz, J_3=6.6Hz, 1H), 2.44-2.36 (m, 2H), 2.34-2.19 (m, 1H), 2.08 (ddd, J_1=9.0Hz, J_2=8.9, J_3=6.8Hz, 1H), 1.85-1.63 (series of m, 4H), 1.61 (s, 3H), 1.55-1.21 (series of m, 4H), 1.16 (s, 3H), 0.90 (d, J=6.9Hz, 3H); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 145.6, 109.8, 57.8, 49.9, 48.1, .47.4, 45.8, 36.3, 33.2, 33.0, 26.0, 24.2, 23.5, 17.7, 14.6; EIMS (75 eV) m/z 204 (M^+).