Abstract: (+)-Kelsoene (1) has been synthesized in 15 steps from commercially available cyclopent-2-en-1-one. Key steps include (a) a methylenecyclopentane annulation of cyclopent-2-en-1-one using the bifunctional cuprate reagent lithium cyano(4-chlorobut-1-en-2-yl)cuprate and (b) a highly stereoselective [2+2]-photocycloaddition of ethylene to the bicyclic enone 10.

Key words: kelsoene, annulation, bifunctional reagent, photocycloaddition, Wilkinson’s catalyst, Lombardo’s reagent

The novel sesquiterpenoid (+)-kelsoene was first isolated from the marine sponge Cymbastella hooperi in 1996 by Wright et al. The following year, König and Wright showed that this natural product has a “most unusual carbocyclic skeleton” and possesses the constitution and relative configuration depicted in 1 (Figure 1). Kelsoene was subsequently isolated from the liverworts Ptychanthus striatus, Tritomaria quinquedentata and Callipogea muelleriana. In 1997, it was reported that the unique tricyclic carbon skeleton of kelsoene is shared by the tetra- and pentacyclic carbon skeletons of kelsoene, annulation, bifunctional reagent, photocycloaddition, Wilkinson’s catalyst, Lombardo’s reagent

Figure 1

In 1999, Nabeta et al. on the basis of 1H NMR experiments carried out on two diastereomeric substances derived from (+)-kelsoene, concluded that the natural product has the absolute configuration shown in 3. However, on the basis of recent synthetic studies carried out by Mehta and Srinivas (vide infra), it is clear that this conclusion was incorrect and that, in fact, the absolute configuration of natural (+)-kelsoene is as depicted in 1.

Owing, no doubt, to its unprecedented structure, kelsoene has recently been the subject of both biosynthetic and synthetic studies. With respect to the synthetic investigations, Mehta and Srinivas have reported routes leading to the preparation of the tricyclo[5.3.0.02,5]decane core of kelsoene, the synthesis of racemic kelsoene and the total syntheses of both (+)- and (-)-kelsoene.

As mentioned above, the latter work showed irrefutably that natural (+)-kelsoene has the absolute configuration shown in structural formula 1.

Notwithstanding its low molecular weight, kelsoene represents a significant synthetic challenge. In addition to its unusual tricarbocyclic skeleton, kelsoene possesses six contiguous carbon chirality centers, of which one is quaternary. Furthermore, the sparsity of functional groups in this substance limits the number of synthetic strategies available. We reasoned that the tricyclic core of kelsoene could be elaborated from the known ketone 6. This functionalized bicyclo[3.3.0]octane was readily prepared by use of a procedure modified from that reported earlier.

As shown in Scheme 1, sequential treatment of 4-chloro-2-trimethylsilylbut-1-ene (4) with MeLi and CuCN-LiCl in THF at −78 °C affords the “lower order” heterocuprate lithium cyano(4-chlorobut-1-en-2-yl)cuprate. Reaction of the latter reagent with cyclopent-2-en-1-one in the presence of BF3-Et2O, followed by a suitable workup procedure, provided the conjugate addition product 5. Intramolecular alkylation of 5 was readily accomplished by treatment of this material with KH in THF.

It appeared likely that hydrogenation of the exocyclic alkene function in 6 would, for sterics reasons, occur predominantly from the convex face of the bicycle. However, treatment of 6 with hydrogen in the presence of Pd/C provided ketones 7 and 8 in nearly equal amounts. Fortunately, use of homogeneous hydrogenation catalysts gave better results. Thus, hydrogenation of 6 using Crabtree’s catalyst furnished 7 and 8 in a ratio of 1:6, but the reaction was very sluggish. On the other hand, reduction of 6 with hydrogen in the presence of Wilkinson’s catalyst afforded a 95% yield of a mixture of 7 and 8, in a ratio of 5:95. These products proved difficult to separate and therefore, were carried through the next synthetic operations as a mixture.

Sequential treatment of the 5:95 mixture of 7 and 8 with LDA and PhSeCl in THF, followed by peroxide oxidation of the resultant α-phenylelenides and chromatographic purification of the acquired material, gave pure enone 9 in 83% yield. Reaction of 9 with MeLi in THF gave the corresponding tertiary alcohol, which, upon treatment with...
was expected to proceed via a transition structure in- enone

In order to complete the synthesis of (±)-kelsoene, it was necessary to use the carbonyl function in 11 to introduce, in a stereoselective fashion, the isopropenyl group. Initial plans called for a one-carbon homologation of ketone 11 to the corresponding aldehyde. However, attempts to initiate this required conversion by subjection of 11 to (potentially suitable) Wittig, Magnus, and Taguchi homologation procedures led either to decomposition of the starting material or provided no reaction at all. The unreactive nature of ketone 11, which can be attributed to the fact that the carbonyl group is sterically hindered, necessitated an alternative approach. In this connection, it has been established that the Lombardo reagent successfully effects methylation of highly hindered ketones. Indeed, addition of a solution of ketone 11 to a suspension of Lombardo’s reagent resulted in the generation of alkene 12 in good yield. Hydroboration of the latter material provided, in 80% yield, a single primary alcohol. Examination of molecular models indicates that hydroboration of alkene 12 should occur primarily from the (less hindered) β-face of the molecule and that, therefore, the resultant primary alcohol should possess the relative configuration shown in 13. Support for this expectation was derived from NMR spectroscopy experiments. The 1H NMR spectrum of 13 could be fully assigned on the basis of HMQC, HMBC, COSY and 13C NMR spectroscopic data. As shown in Figure 2, the secondary methyl group (MeA) in 13 gives rise to a doublet at δ = 1.02, the carbonyl protons Hα and Hβ produce doublet of doublets at δ = 3.33 and 3.93, and the signals due to the tertiary and secondary hydrogens Hc and Hd appear as triplets at δ = 2.30 and δ = 1.34, respectively. In nuclear Overhauser enhancement difference (NOED) experiments, irradiation at either δ = 3.33 or 3.93 (Hα, Hβ) enhances the signal intensities at both δ = 1.02 (MeA) and 2.30 (Hc). Also, irradiation at δ = 3.33 (Hα or Hβ) causes an increase in the intensity of the resonance at δ = 1.34 (Hd). These experiments show clearly that the CH2OH function is on the α-face of the molecule as shown in 13 (Figure 2).

Oxidation of alcohol 13 using tetrapropylammonium per- ruthenate (TPAP) afforded the corresponding aldehyde. The latter substance turned out to be quite unstable and was therefore used shortly after its preparation. Addition of MeLi to the aldehyde and subsequent TPAP oxidation of the resultant diastereomeric mixture of secondary alcohols provided ketone 14 in 86% yield from alcohol 13. At this stage, it was necessary to invert the configuration of the chiral center associated with the acetyl group. This operation was conveniently accomplished by refluxing a bifacial mixture consisting of a deuteriochloroform solution of 14 and a solution of perchloric acid in water.

PCC on alumina was transformed into the required enone 10. The [2+2]-photocycloaddition of ethene to the enone 10 was expected to proceed via a transition structure involving approach of the alkene from the sterically less encumbered face of 10. In the event, this process, which proved to be highly diastereoselective, produced the tricyclic core of kelsoene, with the correct relative configuration at each of the five carbon chirality centers, had been constructed from cyclopent-2-en-1-one in eight synthetic operations.

Scheme 1

Scheme 2

In order to complete the synthesis of (±)-kelsoene, it was necessary to use the carbonyl function in 11 to introduce,
The required substance 15 (epimer of 14) was obtained in 80% yield. Olefination of 15 using Lombardo’s reagent\(^{26}\) furnished, in high yield, (±)-kelsoene (1). The \(^1\)H and \(^13\)C NMR spectral data derived from this material were identical with those published\(^7\) for natural (+)-kelsoene.

In conclusion, (±)-kelsoene (1) was constructed via a 15-step synthetic sequence starting from cyclopent-2-en-1-one and the bifunctional reagent lithium cyano(4-chlorobut-1-en-2-yl)cuprate. The relative configuration of each of the six carbon chirality centers present in the natural product was established with a high degree of stereoselectivity.

Flash chromatography\(^{29}\) was performed using 230–400 mesh silica gel (SiliCycle). IR spectra were determined using neat liquid films through a pad of silica gel (25 g, elution with CH\(_2\)Cl\(_2\)) and the compound was treated with tris(hydroxymethyl)amine (10 mL). The phases were separated and the organic phase was washed (sat. aq NaHCO\(_3\), 10 mL), dried (MgSO\(_4\)) and concentrated. The remaining crude oil was dissolved in CH\(_2\)Cl\(_2\) (20 mL) and the solution was cooled to 0 °C. Aq H\(_2\)O\(_2\) (8.8 M, 1.5 mL, 13 mmol) was added, the mixture was stirred at 0 °C for 1 h and then was treated with 10% aq HCl (10 mL). The phases were separated and the organic phase was washed (brine, 10 mL), dried (MgSO\(_4\)) and concentrated. The crude product was dissolved in CH\(_2\)Cl\(_2\) (20 mL) and the solution was cooled to 0 °C.

Flash chromatography (80 g of silica gel, pentane–Et\(_2\)O, 5:1) of the crude oil provided enone 9 as a colorless oil; yield: 0.755 g (83%).

IR (film): 2953, 2874, 1736, 1459, 1161, 1107 cm\(^{-1}\).

\(^1\)H NMR: \(\delta = 0.97\) (d, 3 H, J = 6.9 Hz), 1.12 (m, 1 H), 1.48 (dddd, 1 H, J = 13.0, 11.4, 8.3, 9.0 Hz), 1.62 (dddd, 1 H, J = 12.7, 6, 6, 3 Hz), 1.77–1.83 (m, 2 H), 1.84 (dddd, 1 H, J = 13.0, 9.4, 3.4, 1.0 Hz), 0.83–1.23 (m, 1 H), 2.17 (ddd, 1 H, J = 17.6, 8.3, 3.4 Hz), 2.25 (dddd, 1 H, J = 17.6, 11.4, 9.4, 1.4 Hz), 2.58 (dddd, 1 H, J = 9, 9, 5.0 Hz), 2.66 (m, 1 H).

\(^13\)C NMR (125 MHz): \(\delta = 14.2, 21.4, 28.8, 32.3, 38.3, 39.6, 45.0, 51.7, 223.1\).

(1R*,5R*,6S*)-4,8-Dimethylbicyclo[3.3.0]oct-3-en-2-one (10)

To a cold (–78 °C) solution of LDA (0.321 M in THF, 25 mL, 8.03 mmol) was added a cold (–78 °C) solution of ketone 8 (0.923 g, 6.69 mmol) in THF (20 mL). The solution was warmed to 0 °C for 30 min and then was recooled to –78 °C. A cold (–78 °C) solution of PhSeCl (1.60 g, 8.35 mmol) in THF (10 mL) was added, the mixture was stirred at –78 °C for 1 h and then was treated with 10% aq HCl (10 mL). The phases were separated and the organic phase was washed (brine, 10 mL), dried (MgSO\(_4\)) and concentrated. The crude product was dissolved in CH\(_2\)Cl\(_2\) (20 mL) and the solution was cooled to 0 °C.

Flash chromatography (80 g of silica gel, pentane–Et\(_2\)O, 5:1) of the crude oil provided enone 10 as a colorless oil; yield: 0.755 g (83%).

IR (film): 2954, 2873, 1707, 1855, 1459, 1353, 1187, 732 cm\(^{-1}\).

\(^1\)H NMR (400 MHz): \(\delta = 0.83–0.91\) (m, 1 H), 1.01 (d, 3 H, J = 7.0 Hz), 1.49–1.57 (m, 1 H), 1.63–1.75 (m, 1 H), 1.84 (dd, 1 H, J = 12.6, 6.4 Hz), 1.97–2.01 (m, 1 H), 2.63 (dd, 1 H, J = 10.4, 5.5 Hz), 3.23 (dddd, 1 H, J = 8, 5.5, 2.7, 2.7 Hz), 6.17 (dd, 1 H, J = 5.8, 2.7 Hz), 7.57 (dd, 1 H, J = 5.8, 2.7 Hz).

\(^13\)C NMR: \(\delta = 15.7, 28.9, 31.3, 36.8, 49.9, 50.2, 135.8, 165.3, 213.7\).

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Conversion of the chloro ketone 5 into the bicyclic ketone 6 was accomplished by treatment of the former substance with KH in THF, as described previously.\(^{14}\)

IR (film): 2953, 1699, 1622, 1439, 1379, 1273, 1190, 882 cm\(^{-1}\).

\(^1\)H NMR (400 MHz): \(\delta = 0.95–1.01\) (m, 1 H), 1.03 (d, 3 H, J = 7.0 Hz), 1.57–1.72 (m, 3 H), 2.01–2.10 (m, 1 H), 2.02 (s, 3 H), 2.60 (dd, 1 H, J = 9.9, 5.6 Hz), 3.08–3.15 (m, 1 H), 5.82–5.84 (m, 1 H).

\(^13\)C NMR: \(\delta = 15.6, 17.5, 27.7, 32.3, 37.0, 50.9, 53.7, 132.4, 179.6, 210.2\).

(1R*,5S*,6S*)-2,8-Dimethyltricyclo[5.3.0.0\(^2\)7]decane-6-one (11)

Enone 10 (37 mg, 0.25 mmol) was dissolved in CH\(_2\)Cl\(_2\) (25 mL) that had been presaturated with ethene (C. P. grade) at –78 °C. The resulting solution was irradiated (–78 °C, 12 h) through a Pyrex filter (\(\lambda > 290\) nm) using a 450-W Hanovia medium pressure mercury arc
10 Hz), 3.93 (dd, 1 H, J = 9, 9 Hz), 1.34 (dddd, 1 H, J = 15.3, 17.4, 23.2, 26.0, 30.0, 32.4, 33.0, 35.8, 47.1, 48.4, 55.0, 55.1, 62.8, 210.0. 

\( \text{IR (film): 3083, 2948, 2869, 1647, 1452, 1374, 886 cm}^{-1} \).

\( \text{13 C NMR: } \delta = 15.3, 17.4, 23.2, 26.0, 30.0, 32.4, 33.0, 35.8, 47.1, 48.4, 55.0, 55.1, 62.8, 210.0. \)

IR film: 2952, 1728, 1455, 1378, 1268, 1160 cm

1H NMR (400 MHz): \( \delta = 0.89 \) (d, 3 H, J = 6.4 Hz), 1.14 (s, 3 H), 1.20–1.30 (m, 1 H), 1.32–1.43 (m, 1 H), 1.45–1.52 (m, 1 H), 1.53–1.63 (m, 3 H), 1.84 (dd, 1 H, J = 19.6, 9.1 Hz), 2.00–2.12 (m, 1 H), 2.18 (dd, 1 H, J = 9, 9.1 Hz), 2.23–2.36 (m, 2 H), 3.21–3.28 (m, 1 H), 4.90–4.95 (m, 2 H).

13C NMR (75 MHz): \( \delta = 167.1, 206.5, 256.7, 279.9, 29.7, 34.6, 34.7, 38.2, 51.0, 54.1, 55.7, 108.8, 159.9. \)

\( \text{1R}^*\text{,2S}^*\text{,5R}^*\text{,6S}^*\text{,7S}^*\text{,8S}^*\text{)-2,8-Dimethyl-6-hydroxy-}

\( \text{methylytricyclo[5.3.0.0}^{2,5}\text{]decane (15) \)

\( \text{To a cold (0 °C) stirred solution of ketone 14 (18 mg, 0.08 mmol) in CDC}1_{3} (3 mL) \)

\( \text{was added 35% aqueous HClO}_4 \) (1 mL) and the resulting biphasic mixture was heated to reflux for 20 h. The reaction mixture was cooled to r.t. and the phases were separated. The organic phase was washed (brine, 3 mL), dried (MgSO\(_4\)) and concentrated. Chromatography (1 g of silica gel, 20:1 pentane–Et\(_2\)O) of the crude oil provided ketone 15 as a colorless oil; yield: 17 mg (95%).

IR film: 2948, 1709, 1452, 1373, 1532, 1155 cm

1H NMR: \( \delta = 0.75 \) (d, J = 6.9 Hz, 3 H), 1.15 (s, 3 H), 1.18–1.27 (m, 1 H), 1.27–1.35 (m, 1 H), 1.35–1.42 (m, 1 H), 1.46–1.57 (m, 1 H), 1.63–1.81 (m, 3 H), 1.81–1.95 (m, 1 H), 2.02 (s, 3 H), 2.05–2.14 (m, 1 H), 2.16–2.29 (m, 1 H), 2.61 (ddd, J = 10.7, 6, 6 Hz, 1 H), 2.89 (ddd, J = 10.7, 8.1, 1 H), 3.21 (ddd, J = 8, 7.3, 8 Hz, 1 H).

13C NMR: \( \delta = 15.3, 17.4, 23.2, 26.0, 30.0, 32.4, 33.0, 35.8, 47.1, 48.4, 55.0, 55.1, 62.8, 201.0. \)

\( \text{IR (film): 2952, 1728, 1455, 1378, 1268, 1160 cm}^{-1} \).

1H NMR: \( \delta = 0.99 \) (d, 3 H, J = 7.3 Hz), 1.04–1.14 (m, 1 H), 1.23 (s, 3 H), 1.47–1.63 (m, 2 H), 1.64–1.79 (m, 3 H), 1.81–1.91 (m, 1 H), 2.09–2.15 (m, 1 H), 2.23–2.37 (m, 3 H), 2.93 (dd, 1 H, J = 9, 9 Hz).

13C NMR: \( \delta = 16.4, 20.9, 21.0, 27.8, 34.1, 35.0, 37.9, 44.0, 51.8, 52.5, 57.9, 225.4. \)

\( \text{IR (film): 3083, 2948, 2869, 1647, 1452, 1374, 886 cm}^{-1} \).

1H NMR: \( \delta = 0.89 \) (d, 3 H, J = 6.4 Hz), 1.14 (s, 3 H), 1.20–1.30 (m, 1 H), 1.32–1.43 (m, 1 H), 1.45–1.52 (m, 1 H), 1.53–1.63 (m, 3 H), 1.84 (dd, 1 H, J = 19.6, 9.1 Hz), 2.00–2.12 (m, 1 H), 2.18 (dd, 1 H, J = 9, 9.1 Hz), 2.23–2.36 (m, 2 H), 3.21–3.28 (m, 1 H), 4.90–4.95 (m, 2 H).

13C NMR (75 MHz): \( \delta = 167.1, 206.5, 256.7, 279.9, 29.7, 34.6, 34.7, 38.2, 51.0, 54.1, 55.7, 108.8, 159.9. \)

\( \text{IR (film): 2952, 1728, 1455, 1378, 1268, 1160 cm}^{-1} \).

1H NMR: \( \delta = 0.89 \) (d, 3 H, J = 7.3 Hz), 1.04–1.14 (m, 1 H), 1.23 (s, 3 H), 1.47–1.63 (m, 2 H), 1.64–1.79 (m, 3 H), 1.81–1.91 (m, 1 H), 2.09–2.15 (m, 1 H), 2.23–2.37 (m, 3 H), 2.93 (dd, 1 H, J = 9, 9 Hz).

13C NMR: \( \delta = 16.4, 20.9, 21.0, 27.8, 34.1, 35.0, 37.9, 44.0, 51.8, 52.5, 57.9, 225.4. \)
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References

(3) Previous literature reports have used different structural numbering systems for kelsoene. In this paper, we have chosen to number the kelsoene skeleton according to IUPAC protocol for tricyclic ring systems.
(28) This experiment was carried out using the CDCl3 solutions that had been employed to record the NMR spectra of compound 14.