

Radical-mediated transannulation reactions in humulene. A new synthesis of substituted bicyclo[6.3.0]undeca-4,9-dienes

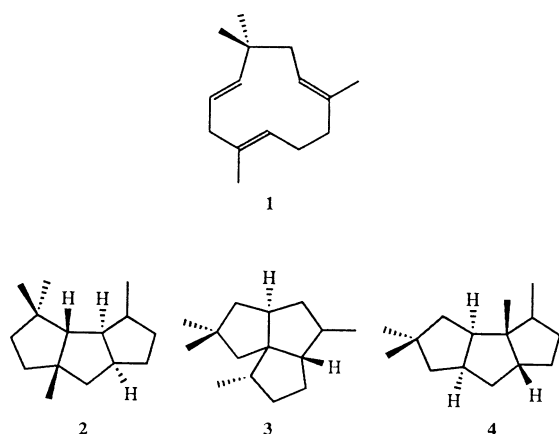
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Alexander J. Blake, Amanda R. Gladwin, Gerald Pattenden* and Allison J. Smithies

Chemistry Department, Nottingham University, Nottingham, UK NG7 2RD

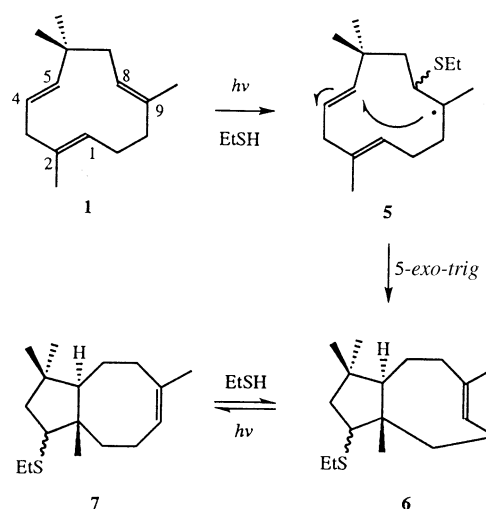
Treatment of the undeca-1,4,8-triene hydrocarbon humulene **1** with ethanethiol radicals results in a facile radical-mediated transannulation producing the sulfide **7** in 50% yield. The structure of **7** follows from its conversion into the bicyclo[6.3.0]undeca-4,9-diene **9** and from an X-ray crystal determination on the di-epoxide **10** derived from **9**.

The 11-membered ring hydrocarbon humulene **1** is a major component of many essential oils, especially hop oil.¹ Its central role as a key intermediate in the biosynthesis of several families of sesquiterpenes, e.g. the triquinanoid capnellanes **2**, pentalenanes **3**, hirsutanes **4**, and also the caryophyllenes, ster-

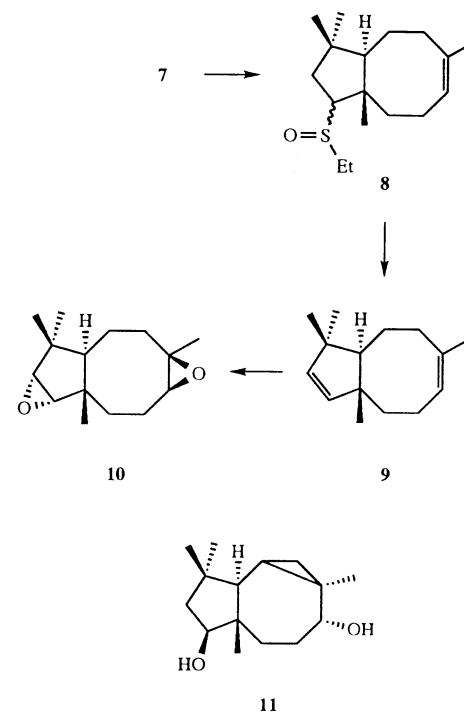


puranes, illudanes and africanes, is well documented.² Furthermore, many of these biosynthetic transannular electrophilic processes have now been mimicked in the laboratory using either humulene itself or one of its three mono-epoxides in the presence of a range of Lewis acids.³ By contrast, radical-mediated transannular reactions involving humulene have not been reported hitherto. In contemporaneous investigations we have described the scope for cascade radical-mediated macrocyclisation-transannular reactions⁴ and for cascade *endo*-cyclisation processes⁵ from polyene precursors in the synthesis of a range of polycycles, including diterpenoids and steroids. We have also described some fundamental radical chemistry of the naturally occurring 14-membered ring diterpene casbene.⁶ We have now examined some radical chemistry of humulene and here we show that treatment of **1** with ethanethiol radicals results in facile transannular cyclisation and formation of the novel 5,8-ring fused bicycle **7**.

Thus, irradiation of a solution of humulene **1** in benzene, using a 300 W ultraviolet sunlamp, in the presence of ethanethiol resulted in the formation of an oily bicyclic product containing one ethylsulfanyl group and one trisubstituted double bond in 50% yield; the remaining material was either polymeric or recovered starting material.⁷ Spectroscopic data alone failed to distinguish between a range of possible ring-fused bicyclic products, and instead we carried out some chemical transformations on the bicyclic sulfide in order to secure more structural



Scheme 1



data. Oxidation of the bicyclic sulfide using potassium periodate led to a mixture of diastereomers of the corresponding

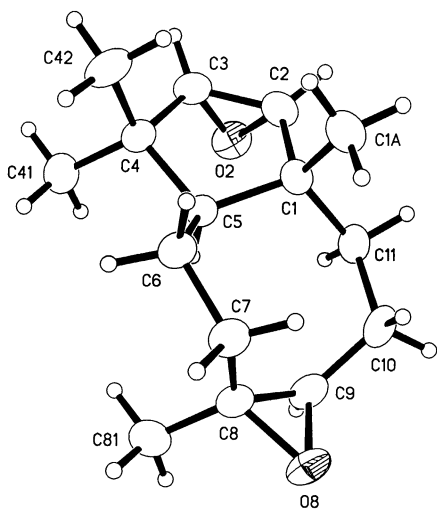


Fig. 1 View of the bis-epoxide **10**. Displacement parameters are drawn at the 30% probability level and H atoms have a small, arbitrary radius for clarity.

sulfoxide which on heating underwent facile elimination of ethanesulfinic acid to produce a bicyclic diene hydrocarbon whose structure was tentatively assigned as **9** from NMR analysis. The full structure and stereochemistry of this hydrocarbon was finally established by carrying out an X-ray analysis of the crystalline di-epoxide **10** derived from it after treatment with *m*-chloroperoxybenzoic acid. The X-ray structure of this di-epoxide is shown in Fig. 1, confirming that its bicyclic diene hydrocarbon precursor did in fact possess the novel bicyclo[6.3.0]undeca-4,9-diene structure **9** shown; the X-ray analysis also established that the bicycle **9** had a *trans* ring junction stereochemistry and that the trisubstituted double bond in the eight-membered ring had the *Z*-configuration.⁸

This study therefore demonstrated that humulene **1** undergoes a facile transannulation reaction in the presence of ethanethiol radicals leading to the substituted 5,8-ring system **7**, which incidentally is structurally similar to that found in the natural sesquiterpene junipediol **11** isolated from *Juniperus formosana* Hayata.⁹ The sulfide **7** presumably results from selective addition of an ethanethiol radical to the C8–C9 double bond in humulene, leading initially to the 11-membered ring radical intermediate **5** (Scheme 1). This is then followed by a facile 5-*exo-trig* transannulation giving rise to the linear and *trans*-ring fused 5,8-bicycle **6**. An addition–elimination of EtS[•] to the trisubstituted double bond in the eight-membered ring of **6** then results in its *E* = *Z* equilibration ultimately leading to the product observed. The *E* = *Z* equilibration could also take place prior to the transannulation reaction **5** → **6** or in concert with it. The absence of other identifiable products from the reaction between humulene and ethanethiol did not allow us to delineate the precise sequence of events between **1** and **7** with any certainty. Further transannulation studies are in progress with other radical initiators and other terpene macrocycles to complement the present study.

Experimental

General details

All melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 1600 series FT-IR instrument as either liquid films or as dilute solutions in spectroscopic grade chloroform. ¹H NMR Spectra were recorded on either a Bruker WM 250 (250 MHz), a JEOL EX-270 (270 MHz) or a Bruker AM 400 (400 MHz) instrument as dilute solutions of deuteriochloroform unless otherwise stated. The chemical shifts are recorded relative to an internal tetramethylsilane standard and the

multiplicity of a signal is designated by one of the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; m = multiplet. All coupling constants, *J*, are reported in Hz. ¹³C NMR Spectra were recorded on either a JEOL EX-270 (67.8 MHz) or a Bruker AM (100 MHz) instrument. The spectra were recorded as dilute solutions in deuteriochloroform unless otherwise stated with chemical shifts reported relative to an internal chloroform standard on a broad band decoupled mode, and the multiplicities obtained using a DEPT sequence. The following symbols are used for the multiplicities in the ¹³C NMR spectra: q = primary methyl; t = secondary methylene; d = tertiary methine and s = quaternary.

Mass spectra were recorded on an AE1 MS-902, an MM-701CF, a VG Autospec or a Micromass 70E using electron ionisation (EI) or fast atom bombardment (FAB) techniques. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

Flash chromatography was performed on Merck silica gel 60 as the stationary phase and all solvents were redistilled before use. All chemical reactions were monitored by thin layer chromatography using Merck silica gel 60F₂₅₄ precoated aluminium plates which were visualised with ultraviolet light and then with either basic aqueous potassium permanganate or acidic alcoholic vanillin.

Routinely, dry organic solvents were stored under nitrogen, and benzene, diethyl ether, toluene and xylenes were dried over sodium wire. Other organic solvents were dried by distillation from the following: THF (sodium benzophenone ketyl), dichloromethane (calcium hydride) and methanol (magnesium methoxide). Organic extracts were dried over anhydrous magnesium sulfate and filtered under gravity. Solvents were removed on a Büchi rotary evaporator. Where necessary, reactions requiring anhydrous conditions were performed in a flame- or oven-dried apparatus under a nitrogen or argon atmosphere.

Humulene was commercially available from Sigma Chemical, Sigma-Aldrich Company Ltd.

(*Z*)-11-Ethylsulfanyl-1,5,9,9-tetramethylbicyclo[6.3.0]undec-4-ene **7**

Ethanethiol (0.5 ml, 6.75 mmol) was added dropwise over 5 min to a stirred solution of humulene (900 mg, 4.4 mmol) in benzene (8 ml), in a sealed tube fitted with a plastic tap. The solution was stirred and irradiated with ultraviolet light from a WOTAN 300 W sunlamp at room temperature for 48 h, and then the benzene was evaporated *in vacuo* to leave a yellow oil. The oil was purified by column chromatography on silica using light petroleum–dichloromethane (10:1) as eluent to give a single diastereomer of the *sulfide* (591 mg, 50%) as a colourless oil; ν_{\max} (film)/cm⁻¹ 824, 758; δ_{H} (400 MHz; CDCl₃) 0.87 (3 H, s, CH₃), 0.91 (3 H, s, CH₃), 0.92 (3 H, s, CH₃), 1.00–1.10 (1 H, m), 1.21 (3 H, t, *J* 7.3, SCH₂CH₃), 1.44–1.52 [3 H, m, CH₂-CHC(CH₃)₂], 1.54 (1 H, m, one of CH₂CHSEt), 1.64 (3 H, s, CH₃), 1.7–2.3 (5 H, m), 2.51 (2 H, q, *J* 7.3, SCH₂CH₃), 2.56–2.57 [1 H, m, one of CH₂C(CH₃)=CH], 2.59–2.61 [1 H, m, CHSEt), 5.41–5.46 [1 H, m, CH=C(CH₃)]; δ_{C} (100 MHz; CDCl₃) 15.2 (q), 15.3 (q), 23.6 (q), 24.0 (t), 25.1 (t), 26.2 (t), 27.8 (q), 29.1 (t), 32.0 (q), 37.9 (s), 41.2 (t), 48.7 (t), 49.8 (s), 51.2 (d), 55.8 (d), 126.0 (d), 135.0 (s); *m/z* (EI) 266.2069 (C₁₇H₃₀S requires *M*⁺, 266.2068), 251 (23%), 205 (28), 189 (21), 149 (27), 135 (34), 123 (100).

(*Z*)-11-Ethylsulfanyl-1,5,9,9-tetramethylbicyclo[6.3.0]undec-4-ene **8**

Potassium periodate (92.5 mg, 0.4 mmol) was added in one portion to a stirred solution of (*Z*)-11-ethylsulfanyl-1,5,9,9-tetramethylbicyclo[6.3.0]undec-4-ene **7** (107 mg, 0.4 mmol) in aqueous acetone (4:1, 100 ml). The solution was stirred at room temperature for 48 h, and then the acetone was removed *in vacuo*. The residue was extracted with diethyl ether (3 × 50 ml) and the combined organic extracts were then dried and

evaporated *in vacuo*. The residue was purified by column chromatography on silica using dichloromethane-diethyl ether (8:1) as eluent to give a mixture of diastereomeric *sulfoxides* (110 mg, 98%) as a colourless oil; ν_{\max} (film)/ cm^{-1} 1047; δ_{H} (400 MHz; CDCl_3) 0.98 [6 H, s, $\text{C}(\text{CH}_3)_2$], 1.26 [3 H, s, $\text{C}(\text{CH}_3)_2$], 1.28–1.34 (3 H, m, SOCH_2CH_3), 1.15–1.56 (6 H, m), 1.64 [3 H, s, $\text{CH}=\text{C}(\text{CH}_3)$], 1.65–2.42 (4 H, m), 2.45–2.75 (4 H, m), 5.39 [1 H, m, $\text{CH}=\text{C}(\text{CH}_3)$]; signals assigned to the major diastereomer δ_{C} (100 MHz; CDCl_3) 7.9 (q), 16.1 (q), 23.4 (t), 24.7 (t), 27.5 (q), 28.8 (t), 33.2 (q), 34.1 (t), 38.4 (s), 43.0 (t), 45.5 (t), 49.3 (s), 52.1 (d), 77.2 (d), 125.3 (d), 135.5 (s); signals assigned to the minor diastereomer δ_{C} (100 MHz; CDCl_3) 6.3 (q), 16.1 (q), 23.7 (q), 24.0 (t), 27.7 (q), 29.6 (t), 32.9 (q), 34.1 (t), 39.5 (s), 40.6 (t), 42.8 (t), 44.8 (t), 51.2 (s), 52.3 (d), 77.2 (d), 126.0 (d), 134.6 (s); m/z (EI) 282.2021 ($\text{C}_{17}\text{H}_{30}\text{SO}$ requires M^+ , 282.2107), 205 (64%), 149 (86), 135 (54), 109 (86), 95 (100), 81 (100).

(Z)-4,8,11,11-Tetramethylbicyclo[6.3.0]undeca-4,9-diene 9

A solution of (Z)-11-ethylsulfinyl-1,5,9,9-tetramethylbicyclo[6.3.0]undec-4-ene **9** (600 mg, 2.1 mmol) in xylene (40 ml) was heated under reflux for 24 h under a nitrogen atmosphere. The mixture was allowed to cool to room temperature and the solvent was then removed *in vacuo*. The residue was purified by column chromatography on silica using pentane as eluent to give the *diene* (196 mg, 43%) as a colourless oil; ν_{\max} (film)/ cm^{-1} 824; δ_{H} (400 MHz; CDCl_3) 0.81 (3 H, s, CH_3), 0.90 (3 H, s, CH_3), 0.97 (3 H, s, CH_3), 1.15–1.40 [2 H, m, $\text{CH}_2\text{C}(\text{CH}_3)$], 1.44–1.64 [3 H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2$], 1.67 (3 H, s, CH_3), 1.89–1.94 [2 H, m, one of $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)$] and one of $\text{CH}_2(\text{CH}_3)=\text{CH}$], 2.02–2.15 [1 H, m, one of $\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)$], 2.52–2.57 [1 H, m, one of $\text{CH}_2\text{C}(\text{CH}_3)=\text{CH}$], 5.22 (1 H, d, J 5.6, $\text{CH}=\text{CH}$), 5.34 (1 H, d, J 5.6, $\text{CH}=\text{CH}$), 5.47 [1 H, app. t, J ~ 8.3, $\text{CH}=\text{C}(\text{CH}_3)$]; δ_{C} (100 MHz; CDCl_3) 20.7 (q), 22.5 (q), 23.0 (t), 23.5 (t), 25.5 (q), 29.0 (q), 29.0 (t), 42.5 (t), 48.0 (s), 51.0 (d), 51.5 (s), 126.0 (d), 136.0 (s), 137.2 (d), 140.0 (d); m/z (EI) 204.1880 ($\text{C}_{15}\text{H}_{24}$ requires M^+ , 204.1878) 189 (13%), 161 (7), 133 (14), 121 (100), 107 (16).

4,5:10,11-Diepoxy-1,5,9,9-tetramethyl-trans-bicyclo[6.3.0]-undecane 10

m-Chloroperoxybenzoic acid (300 mg, 0.98 mmol) was added in one portion to a stirred solution of (Z)-4,8,11,11-tetramethylbicyclo[6.3.0]undeca-4,9-diene **9** (20 mg, 0.10 mmol) in dichloromethane (5 ml) at 0 °C under a nitrogen atmosphere. The resulting mixture was allowed to warm to room temperature where it was stirred for 18 h. Sodium hydrogen carbonate (5 ml, sat. aq.) was added and the mixture was then stirred for a further 12 h. The separated organic layer was washed with sodium hydrogen carbonate (2 × 5 ml) then dried and evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica using pentane as eluent to give the *diepoxide* (17 mg, 73%) as colourless crystals; mp 104–105 °C (pentane) (Found: C, 76.3; H, 10.5. $\text{C}_{15}\text{H}_{24}\text{O}_2$ requires C, 76.2; H, 10.2%); ν_{\max} (CHCl_3)/ cm^{-1} 1382, 907; δ_{H} (400 MHz; CDCl_3) 0.89 (3 H, s, CH_3), 0.94 (3 H, s, CH_3), 1.08 (3 H, s, CH_3), 1.22 (3 H, s, CH_3), 1.23–1.39 (5 H, m), 1.60 (1 H, ddd, J 14.4, 7.2 and 1.4), 1.76–1.82 (1 H, m), 1.89–1.92 (1 H, m), 2.09–2.15 (1 H, m), 2.73 (1 H, dd, J 9.2 and 4.7, CHO), 3.05 (1 H, d, J 2.6, CHO), 3.12 (1 H, d, J 2.6, CHO); δ_{C} (67.8 MHz; CDCl_3) 17.2 (q), 21.1 (q), 21.2 (q), 21.3 (t), 24.7 (q), 24.8 (t), 29.7 (t), 34.3 (t), 42.8 (s), 43.9 (s), 46.7 (d), 59.4 (s), 63.5 (d), 65.5 (d), 67.6 (d); m/z (EI) 236.1776 ($\text{C}_{15}\text{H}_{24}\text{O}_2$ requires M^+ , 236.1776), 203 (23%), 163 (36), 137 (32), 107 (29), 91 (24).

Crystal structure determination

A colourless tablet was mounted on a glass fibre and transferred to the diffractometer.

Crystal data. $\text{C}_{15}\text{H}_{24}\text{O}_2$, $M = 236.34$. Triclinic, $a = 6.3864(6)$, $b = 7.4541(6)$, $c = 15.5454(13)$ Å, $\alpha = 85.834(7)$, $\beta = 83.203(5)$, $\gamma = 67.398(6)^\circ$, $V = 678.10(7)$ Å³ [from 2θ values of 32 reflections measured at $\pm\omega$ ($28 \leq 2\theta \leq 33^\circ$), $\lambda = 0.71073$ Å, $T = 298$

K], space group $P\bar{1}$ (No. 2), $Z = 2$, $D_x = 1.158$ g cm⁻³, colourless tablet $1.1 \times 1.1 \times 0.8$ mm, $\mu(\text{Mo-K}\alpha) = 0.074$ mm⁻¹.

Data collection and processing. Stoe Stadi-4 four circle diffractometer, ω/θ scans with ω scan width $(1.1 + 0.35 \tan \theta)^\circ$, graphite-monochromated Mo-K α X-radiation; 2481 reflections measured ($5 \leq 2\theta \leq 50^\circ$, $\pm h, \pm k, l$), 2385 unique (merging $R = 0.006$), giving 2050 with $F \geq 4\sigma(F)$ and 2376 which were retained in all calculations. No crystal decay was observed and no corrections were applied for absorption.

Structure solution and refinement. Automatic direct methods (all non-H atoms). Full-matrix least-squares refinement with all non-H atoms anisotropic; hydrogen atoms were located from a ΔF synthesis and freely refined with $U_{\text{iso}}(\text{H}) = xU_{\text{eq}}(\text{C})$ [$x = 1.5$ for methyl hydrogens and 1.2 for others]. The weighting scheme $w^{-1} = [\sigma^2(F_o^2) + (0.047P)^2 + 0.143P]$, $P = 1/3[\max(F_o^2, 0) + 2F_c^2]$, gave satisfactory agreement analyses. Final R_1 [$F \geq 4\sigma(F)$] = 0.0365, wR_2 [all data] = 0.1032, $S[F^2] = 1.015$ for 227 refined parameters. An extinction correction refined to 0.0219(11) and the final ΔF synthesis showed no peaks above $\pm 0.18 \text{ e} \text{ \AA}^{-3}$. The figure was produced using SHELXTL/PC.

Atomic co-ordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/94.

Acknowledgements

We thank the EPSRC for a studentship (to A. R. G.) and for the award of a four-circle diffractometer. We also thank Astra Charnwood (studentship to A. J. S.) for support of this work.

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Paper 6/06811A
Received 4th October 1996
Accepted 26th November 1996