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Short Communication

A stereocontrolled total synthesis of (±)-khusimone†

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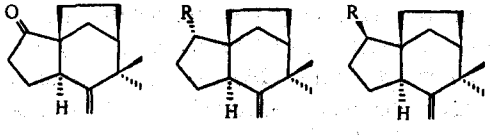
Abstract

A stereocontrolled total synthesis of (±)-khusimone (**1**) has been successfully accomplished involving Wittig olefination of the tricyclic ketone (**17**) as a key step. Intramolecular anionic cyclisation of the indane derivative (**10**) provided the tricyclic dienone (**11**) which was efficiently converted into the mesylate (**15**). Base-induced rearrangement of (**15**) furnished the ketone (**16**) in high yield.

Keywords: Terpene synthesis, intramolecular cyclisation, hydroxylation, rearrangement, Wittig reaction.

Vetiver oil is widely used in high-quality expensive perfumery compositions and soap perfumes. Khusimone (**1**), a norsesquiterpene ketone, is one of the main olfactively important constituents of vetiver oil and was first isolated by Umrani *et al.*[1] Jain *et al.*[2] and Komagata *et al.*[3] reported that **1** shows repellent activity against several pests such as cockroaches, flies, weevils and mosquitoes. Khusimone possesses the tricyclo[6.2.1.$0^{1,5}$]undecane ring system characteristic of the zizaane group of sesquiterpenes and has attracted considerable attention as a challenging synthetic target. The total synthesis of khusimone presents three principal problems: (i) construction of the tricyclo[6.2.1.$0^{1,5}$]undecane ring system with *gem*-dimethyl groups at C-7, (ii) introduction of the exocyclic methylene unit at C-6 and the carbonyl group at C-2, and (iii) control of the stereochemistry of the *trans*-fused hydroindane ring junction. We report herein a stereocontrolled total synthesis of (±)-khusimone starting from the easily accessible indane derivative (**10**). Intramolecular anionic cyclization of **10** provided the tricyclic dienone (**11**) in good yield which was easily converted to the *cis*-diol (**14**) using the functional groups in ring A. Base-induced rearrangement of the corresponding monomesylate



1 **2**, R = CHO; **3**, R = CO_2H **4**, R = CHO; **5**, R = CO_2H

FIG. 1.

†Dedicated to Prof. S. C. Bhattacharyya.
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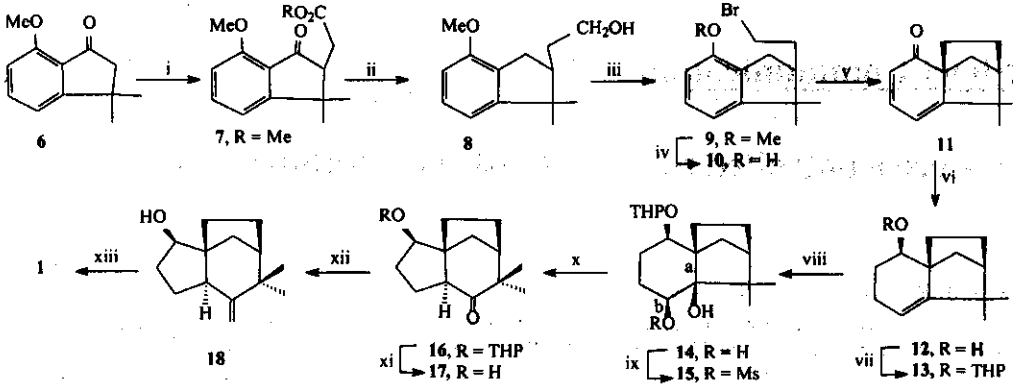
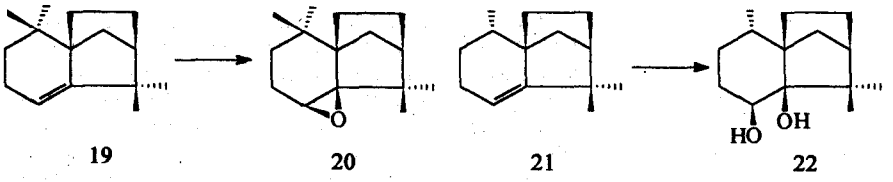


Scheme 1. Reagents and conditions: (i), LDA, $BrCH_2CO_2Et$, THF, –10–20°C: (ii) LAH, Et_2O, reflux; Li, liq.NH_3, NH_4Cl; (iii) Ph_3P, CBr_4, Et_2O, 25°C, (iv) BBr_3,CH_2Cl_2, 0–20°C; (v), *t*-BuOK, *t*-BuOH, 80°C; (vi) $NaBH_4$, EtOH, 0–20°C; (vii) DHP, PPTS, CH_2Cl_2, 20°C; (viii) OsO_4, C_5H_5N, 25°C; (ix) MsCl, C_5H_5N, 10°C; (x) *t*-BuOK, *t*-BuOH, 20°C; (xi) PPTS, EtOH, 55°C; (xii) $CH_3(C_6H_5)_3P^+I^-$, *t*-BuOK, 90°C; (xiii) Jones reagent, $(CH_3)_2CO$. 0°C.

(**15**) afforded the tricyclic ketone (**16**) in high yield which was subsequently converted to (±)-khusimone (**1**). The total syntheses of racemic khusimone were reported earlier by Buchi *et al.*[4] and Oppolzer and Pitteloud[5] and of (-)-khusimone have been accomplished by Liu and Chan.[6] Oppolzer *et al.*,[7] and Sakurai *et al.*,[8] Liu and Chan[6] have converted khusimone into the zizaane sesquiterpenes zizanal (**2**), zizanoic acid (**3**), epizizanal (**4**) and epizizanoic acid (**5**) (Fig. 1). The present work, therefore, constitutes formal total synthesis of the zizaane sesquiterpenes (**2–5**).

Alkylation of 3,3-dimethyl-7-methoxyindanone (**6**)[9] with ethyl bromoacetate using LDA as the base provided the keto-ester (**7**)[10] in 72% yield. Reduction of **7** with $LiAlH_4$ followed by hydrogenolysis of the resulting diol with Li in liquid ammonia afforded the primary alcohol (**8**) in 85% yield. Treatment of **8** with a mixture of Ph_3P and CBr_4 furnished the bromoether (**9**)[11] (80%) which on demethylation with BBr_3 afforded the bromophenol (**10**) (91%). Intramolecular anionic cyclization[12] of **10** using *t*-BuOK as the base provided the tricyclic dienone (**11**)[11] (70%). Reduction[13] of **11** with $NaBH_4$ furnished the alcohol (**12**)[11] (82%), m. p. 117–118°C which was converted to tetrahydropyranyl ether (**13**) (95%). The stereochemical assignments at C-1, C-2 and C-8 of **12** followed from subsequent transformations leading to the keto-alcohol (**17**), the structure of which was established by single-crystal X-ray crystallography of one of its derivatives. Hydroxylation of **13** with OsO_4 furnished the *cis*-diol (**14**) (88%) which was converted into the monomesylate (**15**) in near quantitative yield. The stereochemistries of the hydroxyl groups at C-5 and C-6 have been tentatively assigned β from the following considerations: (i) isolongifolene (**19**) possessing a similar tricyclo[6.2.1.$0^{1,6}$]undecane ring system undergoes epoxidation[14] with perbenzoic acid to yield the β-epoxide (**20**), (ii) hydroxylation of the olefin (**21**) with OsO_4 furnished[15] the *cis*-diol (**22**) as the only product (Fig. 2). The stereostructures of the compounds **20**[16] and **22**[17] have been established by single-crystal X-ray crystallography. The bonds a and b of **15** being antiperiplanar, the mesylate rearranged[18] smoothly on treatment with *t*-BuOK (1 equiv.) at 20°C to afford the ketone (**16**) (88%) which, after removal of the THP group, furnished the keto-alcohol (**17**)[11] (93%), m. p. 89–90°C as the sole product. As mentioned earlier, the relative stereochemistries at C1, C-2, C-5 and C-8 of



19 20 21 22

FIG. 2.

(**17**) were determined by X-ray crystallography[19] of one of its derivatives. Wittig olefination of the ketone (**17**) with methylenetriphenylphosphorane according to a modified procedure[20] afforded the hydroxyolefin (**18**)[11] in 40% yield. Jones oxidation of **18** furnished (±)-khusimone (**1**)[11] (85%). The identity of synthetic khusimone was secured through ^{1}H NMR, ^{13}C NMR, IR and microanalytical data. The structure of **1** was further confirmed from DEPT experiments.

Acknowledgement

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References and notes

1. UMRANI, D.C., SESHADRI, R., GORE, K. G. AND CHAKRAVORTI, K. K. — *Flavour Ind.*, 1970, **1**, 623–624.
2. JAIN, S. C., NOWICKI, S., EISNER, T. AND MEINWALD, J. — *Tetrahedron Lett.*, 1982, **23**, 4639–4642.
3. KOMAGATA, K., OOSAWA, K., YAMAMOTO, I. AND HONDA, H. — Abstracts of papers, *Annual Meeting of the Agric. Chem. Soc. of Japan*, Tokyo 1987, p. 723.
4. BUCHI, G., HAUSER, A. AND LIMACHER, J. — *J. Org. Chem.*, 1977, **42**, 3323–3324.
5. OPPOLZER, W. AND PITTELOUD, R. — *J. Am. Chem. Soc.*, 1982, **104**, 6478–6479.
6. LIU, H. J. AND CHAN, W. H. — *Can. J. Chem.*, 1982, **60**, 1081–1091.
7. OPPOLZER, W., PITTELOUD, R., BERNARDINELLI, G. AND BAETTIG, K. — *Tetrahedron Lett.*, 1983, **24**, 4975–4978.
8. SAKURAI, K., KITAHARA, T. AND MORI, K. — *Tetrahedron*, 1988, **44**, 6581–6588.
9. DAS, S., PAL. A. AND MUKHERJEE, D. — *Tetrahedron Lett.*, 1996, **37**, 4421–4422.
10. Satisfactory spectroscopic and microanalytical data were obtained for all new compounds.
11. Selected spectral data for: **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 3H), 1.32 (s, 3H), 1.90–3.10 (m, 7H), 3.83 (s, 3H), 6.60–6.83 (m, 2H), 7.19 (t, 1H, J = 8 Hz) ; ^{13} C NMR ($CDCl_3$, 75 MHz) δ 23.68, 26.64, 32.01, 32.78, 33.29, 45.91, 49.37, 55.16, 108. 03, 114.44, 128.08, 154.77, 154.77, 155.55. **11**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (s, 3H), 1.19 (s, 3H), 1.50–2.20 (m, 7H), 5.93 (d, 1H, J = 6 Hz), 6.00 (d, 1H, J = 10 Hz), 7.13 (dd, 1H, J = 6 and 10 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.95, 24.65, 27.54, 37.48, 39.06, 43.53, 48.00, 63.15, 109.07, 124.12, 143.96, 172.96, 204.48. **12**: ^{1}H NMR

(CDCl$_3$, 300 MHz) δ 1.00 (s, 3H), 1.06 (s, 3H), 1.20–2.14 (m, 11H), 3.87 (dd, 1H, J = 12 and 6 Hz), 5.14 (t, 1H, J = 3.5 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 24.08, 24.93, 25.28, 25.65, 28.65, 29.05, 40.65, 41.53, 46.98, 54.25, 71.65, 111.10, 155.34. **17**: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.07 (s, 3H), 1.19 (s, 3H), 1.03–2.10 (m, 11H), 2.76 (t, 1H, J = 6.9 Hz), 4.18 (t, 1H, J = 9 Hz); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 17.88, 20.46, 22.08, 25.18, 26.68, 30.77, 36.92, 49.27, 49.85, 53.80, 56.34, 75.17, 215.07. **18**: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.08 (s, 6H), 1.20–1.89 (m, 10H), 2.07–2.18 (m, 2H), 2.38 (t, 1H, J = 9 Hz), 4.12 (t, 1H, J = 9 Hz), 4.57 (bs, 1H), 4.80 (bs, 1 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 20.31, 22.18, 25.42, 26.11, 28.61, 31.48, 37.09, 40.39, 46.97, 48.60, 54.47, 75.92, 105.46, 156.44. **1**: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.09 (s, 3H), 1.10 (s, 3H), 1.15–1.22 (m, 1H), 1.45–1.61 (m, 3H), 1.68–2.06 (m, 5H), 2.17–2.42 (m, 2H), 2.64–2.71 (m, 1H), 4.70 (bs, 1H), 4.87 (bs, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 21.74, 25.61, 25.72, 28.15, 28.43, 35.95, 38.04, 40.65, 47.82, 50.01, 57.78, 106.22, 154.82, 222.32.

12. MURPHY, W. S. AND WATTANASIN, S. — *Chem. Soc. Rev.*, 1983, **12**, 213–250 and references therein.

13. JOHNSON, D. W. AND MANDER, L. N. — *Aust. J. Chem.*, 1974, **27**, 1277–1286.

14. RANGANATHAN, R., NAYAK, U. R., SANTHANAKRISHNAN, T. S. AND DEV, S. — *Tetrahedron*, 1970, **26**, 621–630.

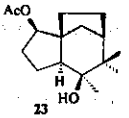
15. PATI, L. C., ROY, A. AND MUKHERJEE, D. — *Tetrahedron Lett.*, 2000, **41**, 10353–10356.

16. MCMILLAN, J. A., PAUL, I. C., NAYAK, U. R. AND DEV, S. — *Tetrahedron Lett.*, 1974, **15**, 419–422.

17. Single-crystal X-ray structure of **22** was obtained through the courtesy of Prof. A. Chakraborty, Department of Inorganic Chemistry, Indian Association for the Cultivation of Science (IACS), Calcutta.

18. GUTSCHE, C. D. AND REDMORE, D. — *Carbocyclic ring expansion reactions*, Academic Press, 1968, pp. 101–103.

19. Single-crystal X-ray structure of the compound **23**, prepared from **17**, was obtained through the courtesy of Dr. W. E. Cleland, Jr, Department of Chemistry, University of Mississippi, USA.



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20. FITJER, I. AND QUABECK, U. — *Synth. Commun.*, 1985, **15**, 855–864.