Short and Selective Total Synthesis of (±)-Khusimone via an Intramolecular Type II "Magnesium-Ene" Reaction

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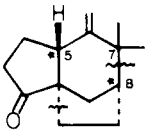
The norsesquiterpene (−)-khusimone, a minor but olfactively interesting constituent of vetiver oil,[1] has been shown to possess structure **1**. Its complex dimethylmethylenetricyclo-



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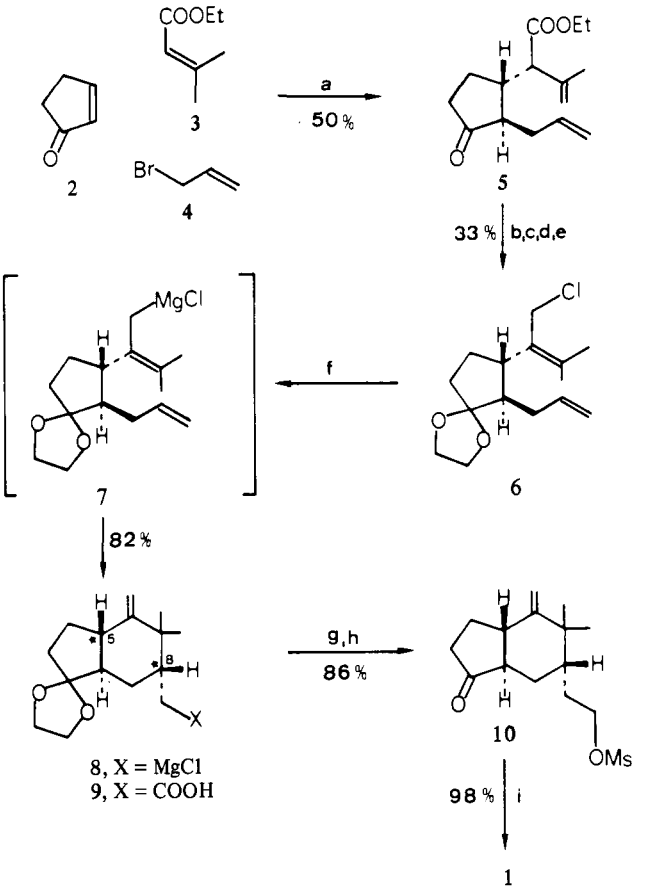
[(6.2.1.0^{1,5})undecane skeleton, common to the sesquiterpenes zizanoic acid, epizizanoic acid, khusimol, and zizaene[2] remains a fascinating challenge to organic synthesis.[3] Apart from degradations of natural zizanoic acid to (−)-**1**[4] two imaginative but nonstereoselective total syntheses of khusimone have been accomplished, by Büchi[5] and Chan.[6] Particular difficulties thereby encountered concerned the relative configuration C(5)–C(8) as well as the positional control over the sterically encumbered exo-methylene group. We describe here a direct, regio- and stereocontrolled total synthesis of (±)-khusimone. In the key step we envisaged to close the bond C(7)–C(8) with concomitant generation of the methylene group by using the methodology presented in the foregoing communication[7] (Scheme I).

Starting from cyclopentenone (**2**) conjugate addition of the dienolate derived from 3,3-dimethylacrylate (**3**) coupled with enolate trapping by alkylation with allyl bromide (**4**) furnished directly the 2,3-disubstituted cyclopentanone **5**[8,9] in 50% yield. Accordingly, all but one of the carbon atoms of **1** have been aligned in a single synthetic operation.[12] **5** was converted to the key

Scheme I[a]



[a] All reactions were carried out under argon. Key: (a) (i) **3** + LDA (1 equiv), THF, −78 °C, 10 min, (ii) rapid addition of **2** (1.05 equiv), slow addition of the resulting solution over 1.5 h to **4** (10 equiv) in 1:2 HMPA–THF, −40 °C (50%); (b) ethylene glycol (10 equiv), TsOH (0.13 equiv), C_6H_6, reflux, 4 h (97%); (c) 1 N NaOEt in EtOH, 60 °C, 4 h (74%); (d) $LiAlH_4$ (2 equiv), Et_2O, 0 °C, 4 h (92%); (e) (i) MsCl (2 equiv), pyridine (2 equiv), 0 °C, 2.5 h, (ii) addition of excess 10% aqueous LiCl, 0 °C, 5 min, (iii) workup with 1 N HCl-ether, 0 °C (51%); (f) (i) slow addition over 1 h of **6** in THF to a stirred suspension of Mg powder (Merck, 3 equiv) in THF, room temperature, (ii) closed Carius tube, 60 °C, 17 h, (iii) passing excess CO_2 into solution, −10 °C, 5 min (82%); (g) $LiAlH_4$ (2 equiv), THF, 0 → 20 °C (92%); (h), (i) MsCl (1.2 equiv), NEt_3 (1.5 equiv), CH_2Cl_2, −10 → 0 °C, 5 min, (ii) stirring with 1 N aqueous HCl-Et_2O, room temperature, 15 h (93%), (i) *t*-BuOK (1.1 equiv), *t*-BuOH/C_6H_6 (1:6) room temperature, 10 min (98%).

precursor **6**[8] by successive protection of the carbonyl group as an ethylene acetal,[8] EtONa-induced olefin migration, reduction of the conjugated ester[8] with $LiAlH_4$, and treatment of the allylic alcohol[8] with MsCl, Py, and LiCl. The unstable allyl chloride **6**, purified by rapid filtration through silica gel, furnished smoothly the Grignard reagent **7** on slow addition to a stirred suspension of commercially available magnesium powder (Merck) in THF. Heating the resulting 0.6 N solution of **7** at 60 °C for 17 h in a closed Carius tube followed by trapping the cyclized organomagnesium chloride **8** with CO_2 at −10 °C furnished, after crystallization (ether–pentane), the carboxylic acid **9**[8] in high overall yield (mp 124–125 °C, 82% from **6**). No isomer of **9** could be found in the mother liquor (^{1}H NMR, GC[13]). Whereas the unidirectional nature of the process **7** → **8** agrees with our previous

(1) Umrani, D. C.; Seshadri, R.; Gore, K. G.; Chakravarti, K. K. *Flavour Ind.* **1970**, *1*, 623. Maurer, B.; Fracheboud, M.; Grieder, A.; Ohloff, G. *Helv. Chim. Acta* **1972**, *55*, 2371.

(2) Nakanishi, K.; Goto, T.; Itô, S.; Natori, S.; Nozoe, S. "Natural Products Chemistry"; Academic Press: New York, 1974; Vol. 1, p 137.

(3) For multistep syntheses of these sesquiterpenes see: Kido, F.; Uda, H.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1969**, *1335*; *J. Chem. Soc., Perkin Trans 1* **1972**, 1755. MacSweeney, D. F.; Ramage, R. *Tetrahedron* **1971**, 1481. Deljac, A.; Mackay, W. D.; Pan, C. S. J.; Wiesner, K. J.; Wiesner, K. *Can. J. Chem.* **1972**, *50*, 726. Coates, R. M.; Sowerby, R. L. *J. Am. Chem. Soc.* **1972**, *94*, 5386.

(4) Maurer, B. Swiss Patent 575 362, 1972; *Ibid.* 583 162, 1974; *Zeitschrift für die Waschmittel-*, Seifen-, *Öl- und Fettindustrie* **1980**, *13*, 347.

(5) Büchi, G.; Hauser, A.; Limacher, J. *J. Org. Chem.* **1977**, *42*, 3323.

(6) Liu, H.-J.; Chan, W. H. *Can. J. Chem.* **1979**, *57*, 708; *Ibid.* **1982**, *60*, 1081.

(7) Oppolzer, W.; Pitteloud, R.; Strauss, H. F. *J. Am. Chem. Soc.*, preceding article in this issue.

(8) IR, ^{1}H NMR (360 MHz), and mass spectra are in full agreement with the assigned structure.

(9) **5** has been assigned the trans configuration in analogy to the stereochemical outcome of the 1,4-addition–alkylation sequence using cyclopentenone and organocuprates[10] or *S*-stabilized organolithium reagents,[11] as well as accounting for the smooth base-induced cis → trans isomerization of 2,3-disubstituted cyclopentanones,[10] see also ref 12.

(10) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.

(11) Seebach, D.; Bürstinghaus, R. *Angew. Chem.* **1975**, *87*, 37; *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 57. Binns, M. R.; Haynes, K. *J. Org. Chem.* **1981**, *46*, 3790.

(12) To our knowledge 1,4-addition of a lithium enolate or dienolate to an enone and direct C-alkylation of the in situ formed enolate adduct has not yet been reported. For the conjugate addition of the lithium enolate of (*S*)-*tert*-butylthioacetate to cyclopentenone coupled with enolate O-silylation followed by regeneration of the enolate and C-alkylation leading to trans-2,3-disubstituted cyclopentanones see: Gerlach, H.; Künzler, P. *Helv. Chim. Acta* **1978**, *61*, 2503.

(13) The mother liquor obtained after crystallization of **9** was esterified (CH_2N_2). GC comparison (capillary column 24 m, OV 101, 220 °C, co-injection) with the ester prepared from crystalline **9** proved the absence of any isomer. Furthermore, quenching of **8** with aqueous NH_4Cl gave a crude hydrocarbon that exhibited a single peak in the GC (glass column, 3 mm i.d. × 3 m, 5% SE 30 on Chromosorb W, 170 °C).

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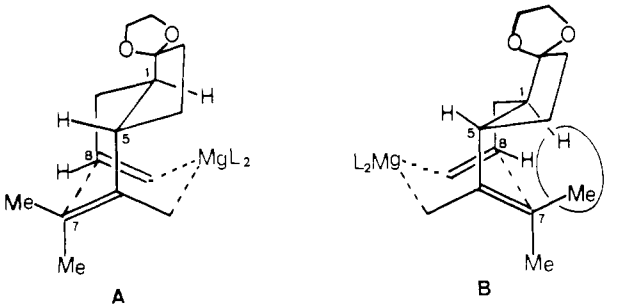
results,[7] its virtually quantitative stereoselectivity is particularly noteworthy. Assuming kinetic stereoselection the alternative transition states A and B have been examined. Indeed, B shows



a boat conformation of the developing cyclohexane, causing severe flagpole repulsion of one C(7) methyl and the C(1) hydrogen, whereas the evolving chair in A is perfectly attainable. We thus predicted A to be favored over B, which entails the desired cis disposition of H–C(5) and H–C(8) in **8**. Unambiguous evidence for this stereochemical assignment was provided by the transformation of **9** into (±)-khusimone as follows. Reduction of the carboxylic acid **9** with $LiAlH_4$, mesylation of the primary alcohol[8] (MsCl, NEt_3), and subsequent acetal cleavage (aqueous HCl, ether) furnished after crystallization the ketomesylate **10**[8] (mp 107.5–108.5 °C, ether–pentane, 86% yield from **9**). Finally, intramolecular alkylation of **10** by brief exposure to *t*-BuOK, *t*-BuOH, and C_6H_6 furnished after sublimation (70–80 °C (bath) (0.04 torr)) pure (±)-khusimone (**1**;[14] mp 72.5–73.5 °C, 98% yield), identified by comparison with authentic (–)-**1** (GC,[15] IR, ^1H NMR, ^{13}C NMR, and MS). In summary, (±)-khusimone was obtained from cyclopentenone by a sequence of nine synthetic operations in 11% overall yield. This strategic application of the remarkably regio- and stereoselective "magnesium-ene" reaction **7** → **8** exemplifies the potential value of this method in synthesis.

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Registry No. (±)-**1**, 64550-95-4; **2**, 930-30-3; **3**, 638-10-8; **4**, 106-95-6; **5**, 83291-58-1; (±)-**6**, 83291-59-2; (±)-**7**, 83291-60-5; (±)-**8**, 83291-61-9; (±)-**9**, 83291-62-7; (±)-**10**, 83291-63-8.

(14) No trace of epikhusimone was detected (^1H NMR) in the crude cyclization product.

(15) GC comparison of (±)-**1** with (–)-**1** was carried out by co-injection using a 24-m capillary column, OV 101, 220 °C.

Action of 2,3-Oxidosqualene Lanosterol Cyclase on 15′-Nor-18,19-dihydro-2,3-oxidosqualene

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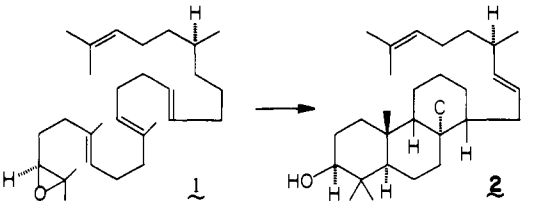
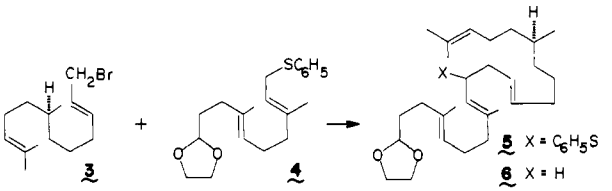
In an endeavor to probe the rigidly enzyme controlled[1] chemistry of ring C formation during lanosterol biosynthesis, the action of 2,3-oxidoxqualene lanosterol cyclase on a particular substrate



1 **2**

variant, 15′-nor-18,19-dihydro-2,3-oxidosqualene (**1**) was investigated. Results summarized herein reveal the final product to be tricycle **2**, presumably generated by hydrogen transfer from the side chain to the C ring of the evolving tricyclic intermediate.

Coupling of trans-bromide **3**[2] and trans,trans-sulfide **4**[2] con-

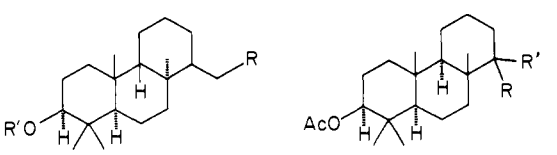


3 **4** **5** X = C_6H_5S **6** X = H

situtes the integral part of the oxide **1** synthesis, accomplished by initial conversion of **4** to its anion with *n*-C_4H_9Li followed by addition of **3** (THF, –78 °C → room temperature). The resulting polyolefinic thioether **5** (69% yield) was then subjected to the action of $Li/C_2H_5NH_2$ at -78 °C, yielding (66%) the acetal **6**. Tritium labeling was carried out by quantitative hydrolysis of the acetal (3% aqueous $HClO_4$/THF, 40 °C) to the parent aldehyde and exposure of the latter to THF/^3H_2O (1 Ci/mL) to which had been added PCl_5. On treatment with $(C_6H_5)_2SC(CH_3)_2$ (THF, –78 °C), the radiolabeled aldehyde was transformed (70%) into epoxide [4-^3H]**1**, purified by prep TLC (specific ^3H activity 6.77 × 10^4 dpm/μg).

The enzymic cyclization was carried out by means of rabbit liver cyclase, as previously described.[3] Incubation of **1** (2.20 mg, 14.9 × 10^7 dpm) at 37 °C for 60 min with a clarified (10.5 × 10^4*g* supernatant) enzyme preparation obtained from the microsomal fraction, followed by denaturization with 1 N methanolic KOH and then ether extraction, gave total product representing 88% recovery of radioactivity. Appropriate boiled controls were carried out. After prep TLC, there were isolated starting material (81%), presumed 2,3-glycol (8%), and a sterol fraction (7%: **2**, R_f 0.28; lanosterol, R_f 0.31), which was purified by HPLC (radioactivity-based percentages of total enzymic product).

High-resolution mass (M^+ 414.3833) and time-averaged 360-MHz NMR (benzene-d_6) spectra indicated that the enzymic product is a polycycle with the same elementary composition as oxide **1** and having an equatorial C-3 hydroxyl (δ 2.98–3.11), five methyls on saturated carbon (0.82–1.06), an isopropylidene unit (1.63, 1.72), and a disubstituted double bond (5.33–5.42). Hydrogenation (Pd/C, EtOAc) afforded a tetrahydro product (*m/e* 418). In order to locate the nonterminal site of unsaturation, oxidative olefin cleavage was carried out with $NaIO_4/OsO_4$ (dioxane/H_2O; 25 °C). High-resolution mass ($M^+ - H_2O$ 288.2455) and NMR spectra revealed the major cleavage product to be a $C_{20}H_{34}O_2$ aldehydro alcohol, resulting from loss of a C_9 side chain fragment. In confirmation of this assignment, $NaBH_4$



7 R = CHO, R′ = H
8 R = CH_2OAc, R′ = Ac

9 R, R′ = O
10 R, R′ = $CHCO_2Et$
11 R = H, R′ = CH_2CH_2OH

(1) van Tamelen, E. E. *Int. Congr. Pure Appl. Chem., 23rd*, **1971**, *5*, 85. van Tamelen, E. E.; Willett, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc.* **1966**, *88*, 5937.

(2) Synthesis to be described elsewhere.

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