155. The Total Synthesis of (±)-Isocomene by an Intramolecular Ene Reaction

Preliminary communication

by **Wolfgang Oppolzer, Kurt Bättig** and **Tomas Hudlicky**

Département de Chimie Organique, Université de Genève, CH-1211 Genève, Switzerland

Dedicated to Professor *Edgardo Giovannini* on his 70th birthday

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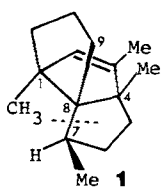
Summary

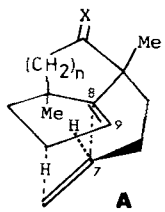
The racemic sesquiterpene isocomene (**1**) has been synthesized starting from 1,7-octadien-3-one (**2**) in a stereoselective manner *(Scheme 2)*. In the key step **4**→**5** the C(7),C(8)-bond was formed by an intramolecular thermal ene reaction. Further elaboration of **5** involved the ring contraction **6**→**7**, the elimination **8**→**9** and the final olefin isomerization **9**→**1**.

Isocomene, isolated from the toxic plant *Isocoma Wrigthii* has been assigned structure **1** by X-ray evidence [1]. The unusual, sterically crowded, poly-fused cyclopentanoid network of this sesquiterpene, involving a tertiary and three quaternary chiral centers[1]) appealed to us as a challenging synthetic target. The recent discovery of more or less related poly-cyclopentanoid natural products such as modhephene [2], retigeranic acid [3], pentalenic acid [4], pentalenolactone H and G [4, 5], quadrone [6], capnellene-tetrol [7], coriolin [8] and hirsutic acid [9] accentuates even more the attraction of synthetic efforts in this field[2]).



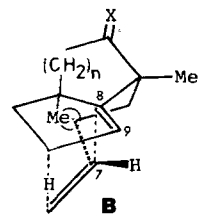
1

ISOCOMENE



A

ENDO



B

EXO
(non bonding interaction)

[1]) To our knowledge the absolute configuration of natural isocomene has not yet been established.

[2]) See for example the synthesis of pentalenolactone G [10]. Further, extensive work illustrates the general interest in the construction of such ring systems [11].

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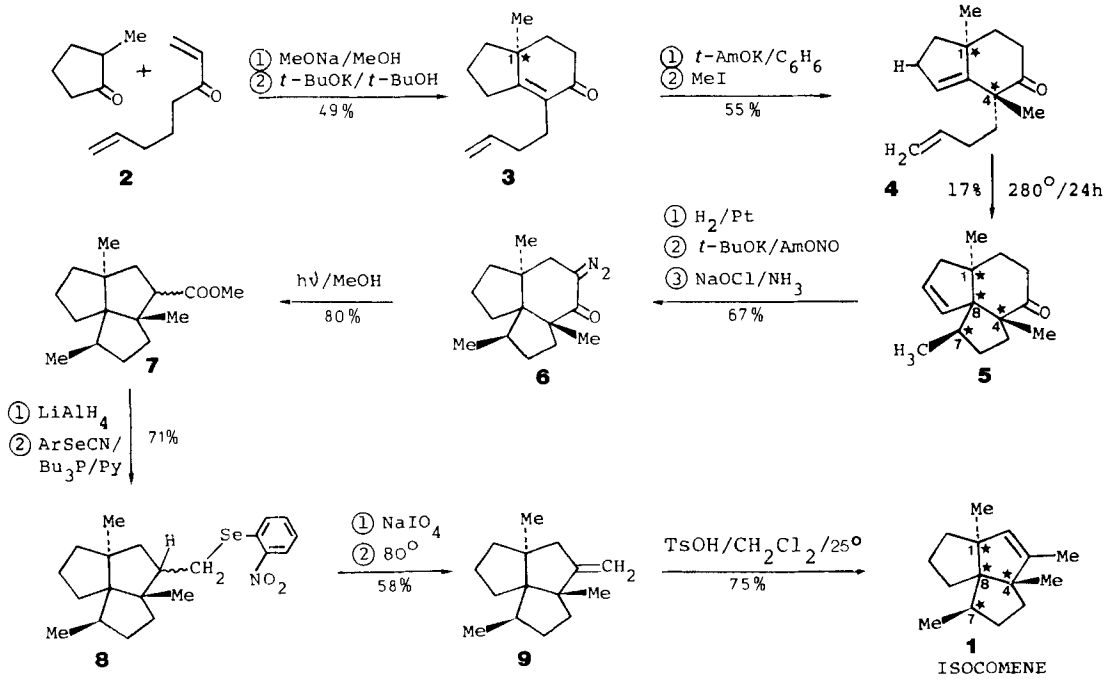
We now wish to report the first total synthesis of (±)-isocomene (**1**), based on the formation of the strategic C(7), C(8)-bond using a stereoselective intramolecular type I-ene reaction[3]). Examination of models of the *endo*- and *exo*-transition states **A** and **B** *(Scheme 1)* shows a severe steric repulsion of the C(1)-methyl and the allylic center of the bridge in the *exo*-orientation **B** and hence the desired *endo*-transition state **A** should be favoured.

Starting from the dienone **2**[4])[5]), *Robinson* annelation [11b] [14] to 2-methylcyclopentanone [1) 2N MeONa in MeOH, −75 to +20°; 2) 0.5N *t*-BuOK in *t*-BuOH, 30°] afforded the bicyclic enone **3**[5]) (b.p. 79–80°/0.1 Torr; IR. (film): 1662, 1645; UV.: 247 (4.06); 49% yield). Methylation of the α,β-unsaturated ketone **3** [15] (1.5 mol-equiv. of potassium 2-methyl-2-butoxide, benzene, 55°, 1 h, followed by addition of 3.0 mol-equiv. of methyl iodide and subsequent heating under reflux of the mixture for 30 min) yielded after chromatography the monomethylated β,γ-unsaturated ketone **4**[5]) (b.p. (bath) 120°/0.04 Torr; IR.: 1705; 55% yield) as the



[3]) For a recent review concerning the classification and applications of intramolecular ene reactions see [12].

[4]) Obtained from 1-bromo-4-pentene in an analogous preparation to that of 1,6-heptadien-3-one [13].

[5]) IR., ^{1}H-NMR. and MS. are in full agreement with the assigned structure. IR. spectra: CCl_4 unless otherwise specified, ν_{max} in cm^{-1}. UV. spectra: EtOH, λ_{max} in nm, log ε in parentheses. ^{1}H-NMR. spectra in $CDCl_3$ at 100 MHz, internal standard tetramethylsilane ($\delta = 0$ ppm), abbreviations: s = singlet, m = multiplet, J = spin-spin coupling constant (Hz).

[6]) The numbering of the centers in this compound corresponds to that of isocomene.

major product together with a minor C(4)-epimer[5][6] (11% yield)[7]). As expected, the intermediate dienolate, derived from **3**, was mainly alkylated on the opposite side to the angular C(1)-methyl group[6]) thus inducing the correct configuration of C(4)[6]) in **4**. This stereochemical assignment correlates with the ^{1}H-NMR. spectra of the separated (GC.) isomers (which show two singlets at 1.21 and 1.23 for the major isomer compared with 1.13 and 1.23 for the minor one) and was ultimately proven by the conversion of **4** to (±)-isocomene. To this end we turned our attention to the crucial ene reaction. Heating the crude 1,6-diene **4** at 280° (2% solution in toluene/24 h) indeed furnished the expected tricyclic product **5**[5])[8]) with high stereoselectivity[9]). The moderate yield of **5** (17%) seems to reflect the steric crowding of this molecule, which allows different reactions to become competitive[9]). Having assembled all four chiral centers correctly it was then necessary to saturate the olefinic bond in **5** and to contract the 6-membered ring. In analogy to established procedures, **5** was treated successively with: 1) H_2 (1 atm), Pd/C, MeOH, 25°; 2) 0.5 N *t*-BuOK (6 mol-equiv.) in *t*-BuOH/*iso*-amyl nitrite (2.5 mol-equiv.), 20°[10]) and 3) sat. aqueous NH_3-solution, 5 N NaOH, aqueous NaOCl-solution, [16] to yield the diazoketone **6**[5]) (IR.: 2090, 1630; UV.: 288 (3.79); 67% overall yield). Irradiation of **6** in methanol [17] (mercury high pressure lamp, quartz apparatus, under N_2) gave the ring-contracted esters **7**[5]) (GC.: 4:1 epimer mixture; IR.: 1730; 80% yield). Reduction of **7** ($LiAlH_4$, ether, 20°) followed by treatment of the resulting primary alcohol[5]) with *o*-nitrophenyl selenocyanate [18] (2 mol-equiv. in pyridine + 2 mol-equiv. of Bu_3P, 20°, 16 h) gave the selenide **8**[5]) (IR.: 1520, 1340; melting at 110–120°; 71% yield). Oxidation of **8** [19] (1.1 mol-equiv. of $NaIO_4$, THF/MeOH/H_2O, 20°, 18 h) followed by thermal fragmentation [20] of the crude selenoxide in refluxing hexane for 30 min[11]) gave the *exo*-methylidene compound **9**[5]) (IR. (CS_2): 882; 58% yield). Finally, acid-catalyzed olefin isomerisation (*p*-toluenesulfonic acid hydrate, CH_2Cl_2, 25°, 3 h) of **9**[12]) followed by filtration of the crude mixture through SiO_2 (CH_2Cl_2) furnished pure (±)-isocomene (**1**) (75% yield) which was identified by comparison with the natural product using GC. (coinjection), TLC. ($SiO_2/AgNO_3$), IR., ^{1}H-NMR. and MS. evidence.

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[7]) The lower homologue 3-(but-3-en-1-yl)-6a-methyl-bicyclo[3.3.0]oct-3-en-2-one could not be methylated under a variety of conditions.

[8]) IR.: 1705; ^{1}H-NMR.: 0.84 (*d*, J = 6, 3 H); 1.02 (*s*, 3 H); 1.18 (*s*, 3 H); 0.8–2.9 (11H); 5.63 (*m*, 1H); 5.90 (*m*, 1H).

[9]) The ene product **5** was isolated by chromatography of the thermolysis mixture ($SiO_2/AgNO_3$, hexane/*t*-butyl methyl ether). Careful analysis of the mixture revealed the presence of structural isomers (15% yield) and of 4,7a-dimethyl-bicyclo[4.3.0]non-3a-en-5-one (resulting from a retro-ene reaction; 22% yield); however no stereosisomers of **5** could be detected.

[10]) The resulting ketoxime[5]) was crystallized from ether/pentane, m.p. 134–136°.

[11]) Usually, alkyl-aryl-selenoxides eliminate spontaneously at 25°; for a recent review on organoselenium chemistry see [21].

[12]) Under these reaction conditions complete isomerization **9** → **1** was observed.

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