Communications to the Editor

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TOTAL SYNTHESIS OF (±)-PENTALENENE

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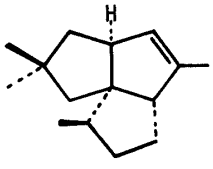
(±)-Pentalenene, the least oxidized triquinane sesquiterpene, was totally synthesized starting from 4,4-dimethyl-2-cyclopenten-1-one via a regioselective C_2-C_8 bond opening of the tricyclo[3.3.0.$0^{2,8}$]octan-3-one intermediate.

KEYWORDS —— regioselective C-C bond cleavage; cyclopropane; pentalenene; sesquiterpene; triquinane; total synthesis

Pentalenene was first isolated from Streptomyces griseochromogenes and designated structure **1**,[1] which represents the parent hydrocarbon of the pentalenolactone family of sesquiterpenoid antibiotics, e.g. pentalenolactone (**2**).[2] The hydrocarbon is also related structurally to the naturally occurring tricyclo[6.3.0.$0^{4,8}$]undecanes, e.g. isocomene (**3**),[3] silphinene (**4**),[4] and senoxydene (**5**),[5] and has been shown to be a biosynthetic precursor of **2**.[2b] Total syntheses of (±)-**1** have been reported by several groups to date.[6] At present we have undertaken synthetic studies on these di- and triquinane sesquiterpenes using the tricyclo[3.3.0.$0^{2,8}$]octan-3-one intermediate (**6**) , via a regioselective C_2-C_8 or C_1-C_2 bond cleavage of **6** as crucial steps. As the first stage, we describe here a total synthesis of (±)-pentalenene (**1**) utilizing a regioselective and reductive C_2-C_8 bond cleavage of the tricyclic intermediate (**6B**) derived from 4,4-dimethyl-2-cyclopenten-1-one (**7**).



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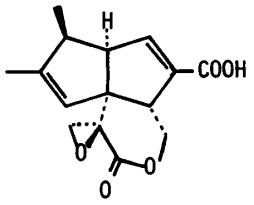

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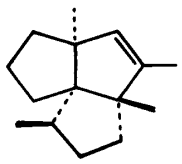

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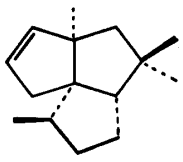

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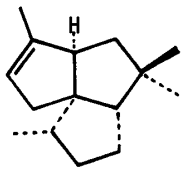

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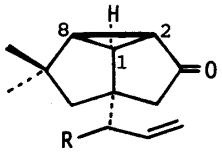
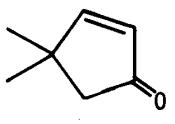


6 A: R=H
B: R=Me



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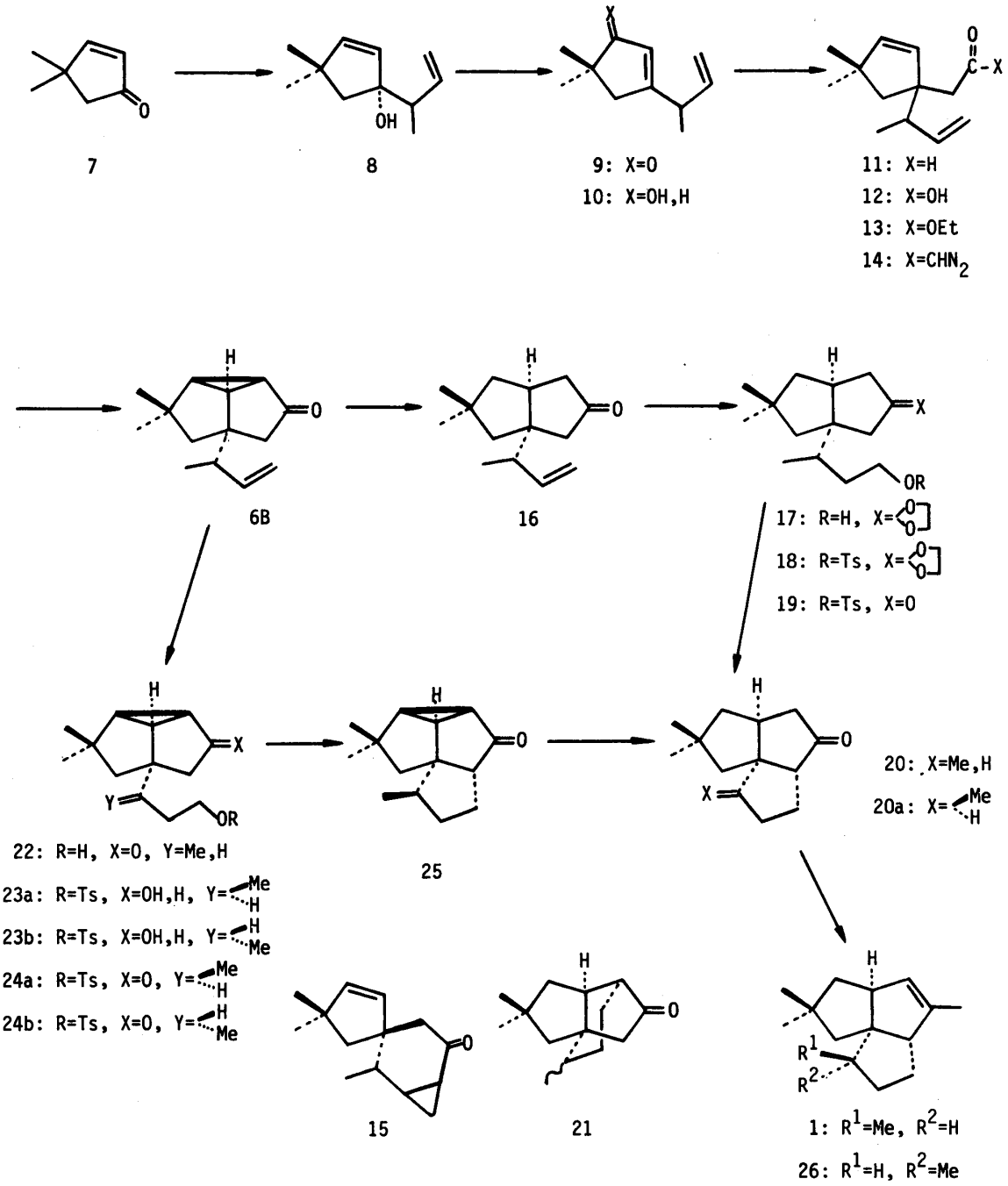
1,2-Addition of crotylmagnesium chloride to the enone (**7**)[7] progressed smoothly under ordinary conditions [in ether at 0°C] to afford quantitatively the tertially allylic alcohol (**8**), which was subsequently subjected to a chromic oxidation.[8] Allylic rearrangement of the hydroxyl group accompanied the oxidation and the desired ketone (**9**)[9] was obtained in 84% yield from the parent enone (**7**). Reduction of **9** with lithium aluminum hydride in ether at 0°C gave the alcohol (**10**) in 99% yield.[10] Treatment of the allylic alcohol with ethyl vinyl ether in the presence of mercuric acetate[11] at 210-220°C in a sealed tube afforded the labile aldehyde (**11**), which was instantly oxidized with the Jones reagent to the carboxylic acid (**12**).[9] The same carboxylic acid (**12**) was also obtainable by an alternative route using the orthoester Claisen rearrangement[12] via **13**. The acid (**12**) was converted into the corresponding diazoketone (**14**) in the usual manner[13] and cyclopropanation of **14** was carried out by treatment with copper bronze in boiling cyclohexane to give exclusively the expected product (**6B**)[9] in 82% yield from **12** without any of the structural isomer (**15**).

A regioselective C_2-C_8 bond cleavage of the cyclopropane ring in **6B** was completed with metal/ammonia reduction. Namely, treatment of **6B** with 7-8 molar equivalents of lithium in liquid ammonia-ether at -78° → -40°C afforded the diquinane product (**16**)[9] in 80% yield. Acetalization of **16** under the usual conditions was followed by a hydroxylation process [hydroboration-oxidation] to give the primary alcohol (**17**) in 73% yield, which was converted into the tosylate (**18**) and then an acidic hydrolysis of **18** afforded the keto tosylate (**19**) in 80% yield from **17**. Cyclization of **19** was achieved by treatment with potassium tert-butoxide in THF at 0°C providing the triquinane product (**20**)[9] in quantitative yield. The structural isomer (**21**) would be also possible for the cyclization product, but its possibility was ruled out by a secure transformation of **6B** into **20** as follows. Although a chemoselective hydroboration of **6B** followed by oxidation with alkaline hydroperoxide afforded the keto alcohol (**22**) in 45% yield, the same reaction using excess diborane and the subsequent tosylation provided two diastereomeric alcohol-tosylates (**23a**[9] and **23b**[9]) in 23 and 24% yield, respectively.[14] Each of these was oxidized to the corresponding ketone [**24a**[9] (100%) or **24b**[9] (100%)], the former one was cyclized under the same conditions mentioned above to give **25** in 95% yield. Finally, reductive cyclopronane ring cleavage of **25** by means of the conditions employed for **6B** afforded the triquinane (**20a**)[9,15] in 78% yield.

Reaction of **20a** with methyllithium in ether at 0°C and the subsequent dehydration with p-TsOH in boiling benzene provided (±)-pentalenene (**1**)[9] in 62% yield, while the same treatment of **20** gave a 1.8:1 mixture of (±)-**1** and (±)-epipentalenene (**26**),[6d,9] which were separable from each other by chromatography on 10% silver nitrate impregnated silica gel,[6d] in 77% yield. The synthetic pentalenene was proved to be identical with the authentic sample[1] by means of spectral comparison.

Thus, a novel route to triquinane sesquiterpenes, illustrated as total synthesis of (±)-pentalenene (**1**), has been established by a regioselective and reductive cleavage of the cyclopropane ring in the tricyclo intermediate (**6**). Further applications of this method to the synthesis of other products are now in progress.



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9) IR and NMR spectra were measured in CCl_4 solution unless otherwise stated. Representative characterization data include: **9** δ: 1.02 (6H,s), 1.30 (3H,d,J=7Hz), 2.40 (2H,m), 3.14 (1H,m), 4.8-5.3 (2H,m), 5.5-6.2 (2H,m), ν: 1710, 1610, m/z: 164 (M^+); **12** δ($CDCl_3$): 0.93 and 0.97 (total 3H,each d,J=7Hz), 1.08 (6H,s), 1.71 (2H,s), 2.42 (2H,s), 4.7-5.2 (2H,m), 5.2-6.0 (1H,m), 5.42 (2H,s), 10.20 (1H,br), ν($CHCl_3$): 3500-2400, 1710, m/z(CI): 209 (M^++1); **6B** δ: 1.00 and 1.03 (total 3H,each d,J=7Hz), 1.10, 1.20, and 1.21 (total 6H,each s), 4.8-5.2 (2H,m), 5.2-6.0 (1H,m), ν: 1720, 1640, 995, 920, m/z: 204 (M^+); **16** δ: 0.95 and 1.00 (total 3H,each d,J=7Hz), 1.02 (3H,s), 1.07 (3H,s), 4.8-5.2 (2H,m), 5.2-5.9 (1H,m), ν: 1740, m/z: 206 (M^+); **20** δ: 0.95 (3H,d,J=7Hz), 1.00, 1.03, and 1.09 (total 6H,each s), ν: 1740, m/z: 206 (M^+); **20a** δ: 0.95 (3H,d,J=7Hz), 1.00 (3H,s), 1.09 (3H,s), ν: 1740, m/z: 206 (M^+); **23a** δ($CDCl_3$): 0.80 (3H,d,J=7Hz), 1.13 (3H,s), 1.35 (3H,s), 2.42 (3H,s), 4.0-4.3 (2H,m), 4.7-5.0 (1H,m), 7.30 (2H,d,J=8Hz), 7.74 (2H,d,J=8Hz), ν($CHCl_3$): 3600, 1600, m/z: 378 (M^+); **23b** δ($CDCl_3$): 0.74 (3H,d,J=7Hz), 1.11 (3H,s), 1.34 (3H,s), 2.44 (3H,s), 3.9-4.3 (2H,m), 4.7-5.0 (1H,m), 7.33 (2H,d,J=8Hz), 7.78 (2H,d,J=8Hz), ν($CHCl_3$): 3600, 1600, m/z: 378 (M^+); **24a** δ($CDCl_3$): 0.86 (3H,d,J=7Hz), 1.08 (3H,s), 1.20 (3H,s), 2.45 (3H,s), 4.0-4.3 (2H,m), 7.33 (2H,d,J=8Hz), 7.78 (2H,d,J=8Hz), ν: 1720, 1600, m/z: 376 (M^+); **24b** δ($CDCl_3$): 0.86 (3H,d,J=7Hz), 1.07 (3H,s), 1.18 (3H,s), 2.42 (3H,s), 4.0-4.3 (2H,m), 7.33 (2H,d,J=8Hz), 7.78 (2H,d,J=8Hz), ν: 1720, 1600, m/z: 376 (M^+); (±)-**1** ^{1}H-NMR δ($CDCl_3$): 0.89 (3H,d,J=7Hz), 0.98 (6H,s), 1.60 (3H,br), 2.3-2.8 (2H,m), 5.14 (1H,m), ^{13}C-NMR δ($CDCl_3$): 15.52, 17.03, 27.71, 29.22, 30.05, 33.66, 40.63, 44.73, 46.97, 49.07, 59.50, 62.23, 64.91, 129.61, 140.68, m/z: 204 (M^+); **26** ^{1}H-NMR δ($CDCl_3$): 0.93 (3H,d,J=7Hz), 0.97 (6H,s), 1.61 (3H,br), 2.5-2.7 (1H,m), 2.7-3.0 (1H,m), 5.16 (1H,m), ^{13}C-NMR δ($CDCl_3$): 13.41, 15.26, 28.52, 29.16, 31.50, 32.96, 39.69, 45.00, 46.17, 50.51, 54.75, 63.38, 63.92, 131.30, 140.58, m/z: 204 (M^+).
10) Obtained as an inseparable mixture of two diastereoisomers.
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14) Separation of the isomers was easily accomplished by means of silica gel chromatography.
15) GLC (OV-17) and ^{1}H-NMR spectral comparison shows that **20a** is identical with one component of diastereoisomers of **20**.

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