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A 4+3 cycloaddition approach to the spatane ring system

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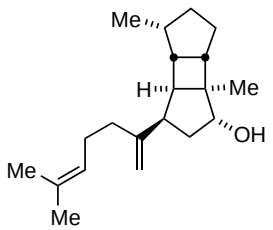
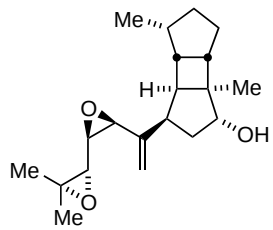
Abstract—The adduct of dichloroketene and cyclopentene was converted to a tricyclo[5.3.0.0^{2,6}]decane ring system using a 4+3 cycloaddition reaction followed by a quasi-Favorskii rearrangement as the key steps. © 2001 Elsevier Science Ltd. All rights reserved.

The 4+3 cycloaddition reaction is a powerful method for the preparation of seven-membered and larger rings.[1] We have been involved in various studies of this reaction and have recently turned our attention to the cycloaddition reaction of halogenated, cyclic allylic cations with dienes.[2] For example, we reported that treatment of 2,5-dibromocyclopentanone (**1**) with triethylamine in the presence of furan in a 1:1 mixture of trifluoroethanol and ether as solvent resulted in the formation of the cycloadduct **2**.[2b] Reaction with methyllithium afforded the alcohol **3** in 65% yield for the two steps. Treatment of this compound with potassium hydride in THF led to the ketone **4** in 72% yield (Scheme 1). This quasi-Favorskii rearrangement is of interest in that it allows dibromocyclopentanone to function as an equivalent of a substituted cyclobutene.[3]

In an effort to further explore this methodology, we have initiated a program involving the formal or total synthesis of cyclobutane-containing natural products. One class of such compounds includes the spatane diterpenes, represented by stoechospermol (**5**) and the antitumor agent spatol (**6**).[4] A number of approaches to these types of compounds have been reported, including several total syntheses.[5] Our goal was to demonstrate that we could build the spatane skeleton using a 4+3 cycloaddition reaction coupled to a quasi-Favorskii rearrangement. This would establish the utility of more complex cyclopentenyl cations in the 4+3 cycloaddition reaction and also allow us to examine the potential of the adducts to undergo nucleophilic attack and subsequent quasi-Favorskii rearrangement.

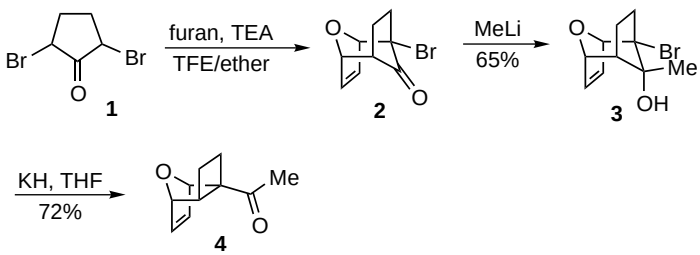


5, stoechospermol



6, spatol

We began with the dichloroketene adduct of cyclopentene (**7**).[6] Based on our previous results, we would have preferred to use the corresponding dibromo compound. However, we have had some difficulty handling some dibromocyclobutanones and cyclopentanones and anticipated that the dichloro compounds would be



Scheme 1. 2,5-Dibromocyclopentanone as a cyclobutene equivalent.

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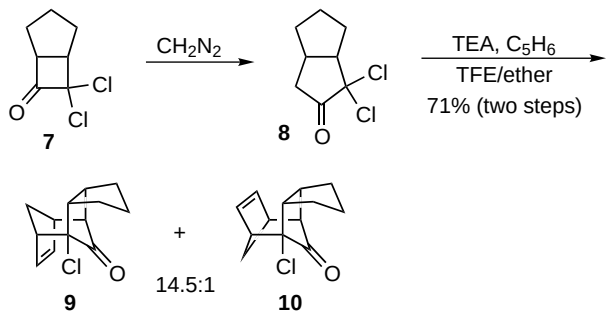
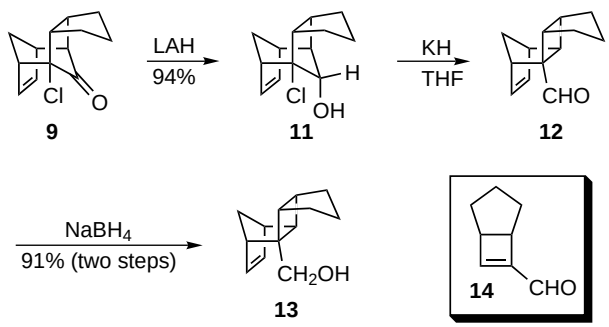
more stable. Given that our work with chloroketones with respect to their quasi-Favorskii reaction was quite limited,[2b] this offered us an opportunity to demonstrate that using chlorinated precursors in our sequence could be effective with respect to both cycloaddition and subsequent rearrangement chemistry.

Treatment of **7** with diazomethane afforded the ring expanded product **8**.[7] This was immediately reacted with cyclopentadiene in the presence of triethylamine in trifluoroethanol/ether to give the cycloadducts **9** and **10** in 71% yield from **7** in a ratio of 14.5:1 (Scheme 2). The ratio was determined by examination of the crude reaction mixture by ^{1}H NMR. The stereochemical assignment was based on differences in the chemical shift of the olefinic protons in **9** and **10**. In **9**, the olefinic protons appear at 6.25 ppm while those of **10** appear at 6.57 ppm. The upfield shift of the protons in **9** can be ascribed to their being in the shielding cone of the ketone carbonyl group. This feature is absent in **10**. The *endo* stereochemistry was thus assigned to **9**. Based on other cycloadditions of related cationic species,[8] this result was not unexpected, though it was pleasing to find that the chloro substituent had no untoward effect on the outcome of the reaction.

The major cycloadduct **9** was reduced with lithium aluminum hydride to afford the corresponding alcohol **11** with complete stereoselectivity in 94% yield. The stereochemistry of **11** was established by X-ray crystallography. Assuming the reaction proceeds by nucleophilic addition, hydride attack does occur on the face of the carbonyl group which is least sterically hindered, based on an inspection of models. Reaction of **11** with potassium hydride in THF at room temperature gave the aldehyde **12**. Reduction of the aldehyde with sodium borohydride gave the ring-contracted alcohol **13** in 91% yield over two steps (Scheme 3). This sequence demonstrates that ketone **8** is synthetically equivalent to cyclobutene **14**.



Scheme 2. 4+3 cycloaddition reaction of **8**.



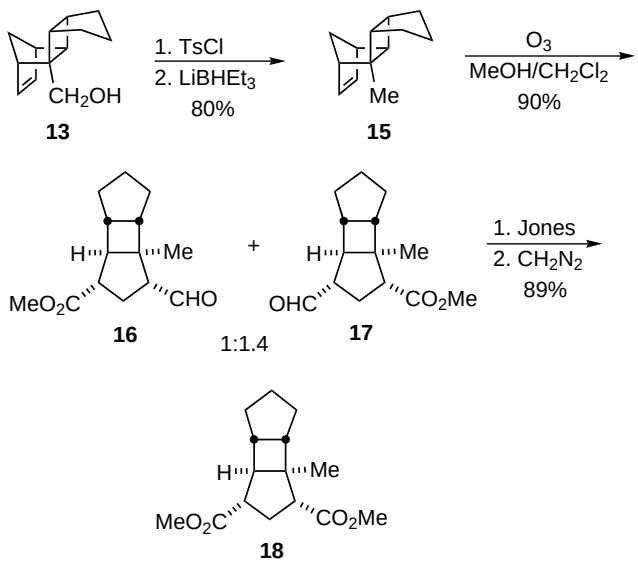
Scheme 3. Quasi-Favorskii rearrangement of **9**.

The aldehyde produced in the quasi-Favorskii reaction could be reduced directly via a Wolff–Kishner reduction but the yields thus far have been less than 50%. We thus treated alcohol **13** with tosyl chloride and reduced the resulting ester with lithium triethylborohydride.[9] This gave the alkene **15** in 80% overall yield.

Finally, in order to demonstrate that the spatane ring system could be produced, we ozonized **15** using a protocol introduced by Schreiber and co-workers.[10] This afforded the two regioisomeric ester aldehydes **16** and **17** in 90% overall yield in a ratio of 1:1.4 (Scheme 4). These regioisomers were separated and structural assignments were made on the basis of NOE data.

For example, the aldehyde proton of **16** showed a crosspeak with the aliphatic methyl group on a 2D NOESY spectrum. This signal was absent from the spectrum of **17**. Furthermore, when a mixture of **16** and **17** was oxidized and esterified, only the diester **18** was isolated, suggesting that **16** and **17** are not epimers.

In summary, we have shown that the combination of a 4+3 cycloaddition reaction followed by a quasi-Favorskii rearrangement can provide rapid access to the spatane ring skeleton. Efforts to apply chemistry of this type to the total synthesis of diterpenes of the spatane class, including spatol, are underway. Progress will be reported in due course.[11,12]



Scheme 4. Formation of the spatane skeleton from **13**.

Acknowledgements

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11. Data for selected compounds: (**9**): Colorless oil, ^{1}H NMR (300 MHz) δ 6.31–6.21 (m, 2H), 3.04–3.03 (m, 1H), 2.82–2.80 (m, 1H), 2.73–2.64 (m, 1H), 2.54–2.46 (m, 1H), 2.34 (s, 1H), 2.31 (d, $J=7.6$ Hz, 1H), 2.00–1.90 (m, 1H), 1.87–1.63 (m, 3H), 1.50–1.24 (m, 2H), 1.16–1.03 (m, 1H); ^{13}C NMR (75.5 MHz) δ 205.0, 139.1, 136.1, 80.4, 55.6, 53.3, 47.6, 44.1, 43.3, 39.3, 32.7, 30.7, 27.7; IR (Neat) 3015, 2925, 1756, 1435, 729 cm^{-1}; Anal. calcd for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79. Found: C, 70.23; H, 6.86. (**13**): White solid, mp 95–97°C; ^{1}H NMR (250 MHz) δ 6.16–6.13 (m, 1H), 6.02–5.99 (m, 1H), 3.67 (d, $J=11.1$ Hz, 1H), 3.08 (d, $J=11.1$ Hz, 1H), 2.79 (d, $J=1.1$ Hz, 1H), 2.64 (t, $J=1.2$ Hz, 1H), 2.27 (t, $J=7.0$ Hz, 1H), 2.03–1.77 (m, 4H), 1.74–1.63 (m, 1H), 1.61–1.45 (m, $J=3$H), 1.35–1.30 (m, 2H), 1.03 (t, $J=1.3$ Hz, 1H); ^{13}C NMR (62.9 MHz) δ 136.7, 135.1, 62.7, 49.2, 45.6, 45.3, 43.9, 42.7, 41.2, 39.6, 31.9, 29.2, 27.6; IR (CH_2Cl_2) 3493, 2983, 2874, 1389, 1129 cm^{-1}; Anal. calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 82.18; H, 9.39. (**18**): White solid, mp 46–47°C; ^{1}H NMR (250 MHz) δ 3.67 (s, 3H), 3.66 (s, 3H), 2.92 (t, $J=8.9$ Hz, 1H), 2.74 (td, $J=3.9$, 8.5 Hz, 1H), 2.54 (t, $J=7.3$ Hz, 1H), 2.42 (q, $J=6.1$ Hz, 1H), 2.29–2.22 (m, 2H), 1.97 (t, $J=4.4$ Hz, 1H), 1.83–1.56 (m, 4H), 1.46–1.35 (m, 2H), 0.82 (s, 3H); ^{13}C NMR (62.9 MHz) δ 175.5, 173.7, 57.0, 52.1, 51.7, 51.2, 50.9, 47.5, 46.1, 43.8, 33.8, 31.7, 27.3, 26.2, 15.5; IR (CH_2Cl_2) 3027, 2950, 1733, 1439, 1220, 1171 cm^{-1}, Anal. calcd for $C_{13}H_{18}O$: C, 67.64; H, 8.33. Found: C, 67.49; H, 8.19.
12. All new compounds exhibited satisfactory ^{1}H and ^{13}C NMR and IR spectral data as well as satisfactory combustion analysis or high resolution exact mass data.