Stereoselective Synthesis of Alcohols, XLVI[1]

Synthesis of a Hydroxytrioxaadamantane, a Model for the Trioxaadamantane Moiety of Muamvatin

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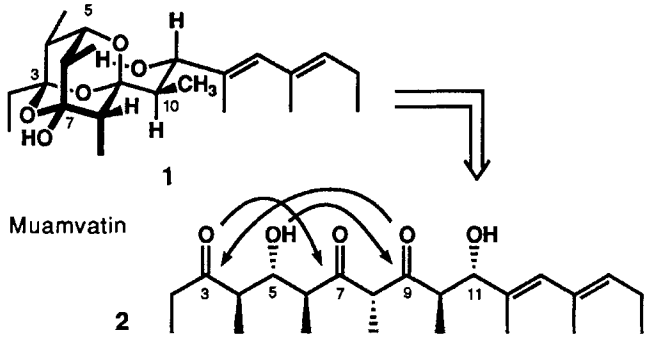
A protected hydroxy triketone **22** has been generated by direct Swern oxidation of a δ-trimethylsilyloxy alcohol **11**, avoiding the formation of a δ-hydroxy ketone as an intermediate. Conditions have been worked out, which allow the deprotection of a *tert*-butyldimethylsilyl group and the spontaneous tricyclization of the resulting hydroxy triketone **4** to an acid-sensitive hydroxytrioxaadamantane **5**.

Muamvatin (**1**) is a marine natural product which has been isolated from *Siphonaria normalis* by the group of Ireland[2]. Important clues to its structure, i.e. the relative configuration at C-3 to C-9, were based on detailed NMR investigations. We secured the absolute configuration by a stereoselective synthesis of a degradataion product[3]. Finally, the complete structure has been verified by Paterson[4] who succeeded in performing the first total synthesis of muamvatin.

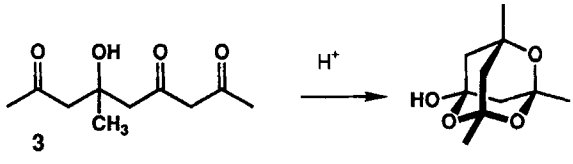
Scheme 1



The most conspicuous part of muamvatin is its trioxaadamantane moiety which is unusual for a natural product and is potentially an artifact[4] of the isolation procedure. It is likely that this moiety arises either biologically or during workup from a polyketide precursor **2** in a sequential acetalization process. Such a process has precedent in the acid-induced tricyclization of the hydroxy triketone **3**, observed by Agback[5].

It could be anticipated that the cyclization of a muamvatin precursor such as **2** would, in contrast to **3**, require very delicate conditions in order to avoid condensation reactions with loss of water. In the present paper, we describe our model studies of the generation of the trioxaadamantane unit present in muamvatin. These studies were carried out with racemic materials.

Scheme 2



Principal Considerations

By a model study aimed at the cyclization of **4** to **5** we hoped to learn how to handle the functional group intricacies present in **4** and its precursors. We anticipated that the configuration at C-8 of **4** will scramble as soon as C-7 and C-9 carry simultaneously a carbonyl function. Thus, the C-9 carbonyl function in **6** has to be protected before C-7 is oxidized.

Once C-7 is oxidized, subsequent oxidation at C-3 meets with difficulties, because a free C-3 hydroxyl group would add to the C-7 carbonyl group to form a pyranose derivative, preventing the intended oxidation at C-3. This difficulty would remain even if C-3 were oxidized first, because as soon as the C-7 hydroxyl group is liberated, it would, in turn, add to the C-3 carbonyl group, thus preventing oxidation at C-7. This detrimental pyranose formation between C-3 and C-7 can perhaps be avoided, if C-3 and C-7 are held sufficiently apart in space. Such a situation could be generated, if another pyranose ring is installed, (cf. **7**), i.e. between C-5 OH and the C-9 carbonyl group, a strategy also used by Paterson[4]. It can be anticipated that the equatorial disposition of the C-4 side chain holds C-3 far apart from C-7. Moreover, if C-3 were oxidized first, an interaction with the C-7 hydroxyl group would be impossible, if the latter were *trans* to C-4. On the basis of these consider-

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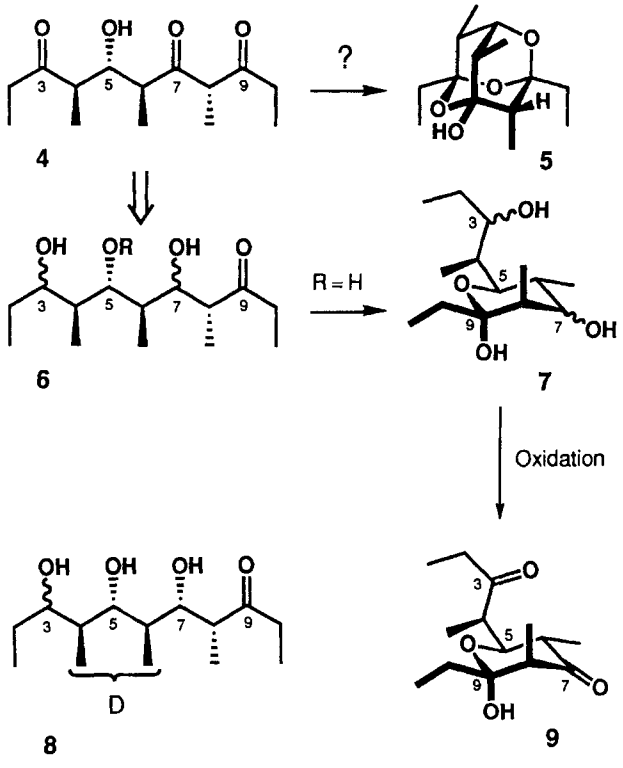
ations the most attractive precursor molecule would be the trihydroxy ketone **8**.

The designed intermediate **7** has the additional advantage that it internally protects the C-9 carbonyl function as required to maintain the stereochemical integrity at C-8 during oxidation at C-7.

Scheme 3



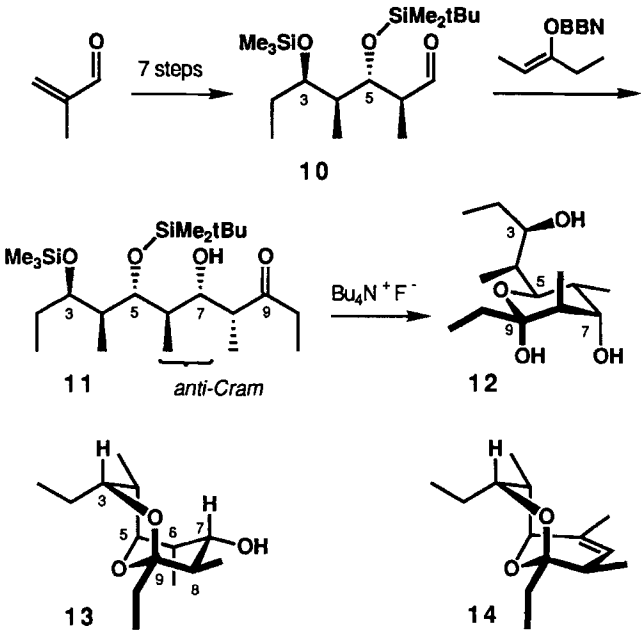
4 **5** **6** **7** **8** **9**

The C-5/C-9 Internally Protected Intermediate 9

The starting material **8** contains the stereotriad D[6], which is the most difficult one to be generated from the four possible stereotriads. Recent efforts led to an improved synthesis of several building blocks containing the stereotriad D[1]. In view of the present study, we developed a seven-step conversion of methacrolein into the building block **10**[1].

The task was to convert **10** into the *syn* aldol **11**. The aldol addition with (*Z*)-enol borinates is known to provide reliably *syn* aldols[7,8]. In our case, the *anti*-Cram adduct was required. Previous studies indicated that on addition to aldehydes such as **10**, which exhibit an (in this case 5,6-)-*anti*-substitution pattern, there is a preference for the formation of the *anti*-Cram adduct[1,9]. By reaction of the aldehyde **10** with 2 equivalents of the enol borinate derived from 9-BBN triflate and diethyl ketone[8] we obtained in 85% yield a single diastereomeric aldol. The *syn* disposition at the two newly formed stereocenters C-7 and C-8 followed from the small (J = 2.5 Hz) coupling constant between 7-H and 8-H in the ^{1}H-NMR spectrum. The relative configuration at C-6/C-7, i.e. the *anti*-Cram preference of the aldol addition, was established by analysis of the bicyclic ketal **13** (see below).

Scheme 4



10 **11** **12** **13** **14**

Fluorodesilylation with tetrabutylammonium fluoride liberated the trihydroxy ketone **8** which cyclized spontaneously to the tetrahydropyranol **12** in 92% yield. When the latter was treated with *p*-toluenesulfonic acid in methanol in an attempt to generate the methyl ketal of **12**, we instead obtained two bicyclic ketals **13** (69%) and **14** (23%). The formation of **13** was fortunate at least in so far as it allowed the clear-cut identification of the relative configuration at C-6, C-7, and C-8. First, a NOESY experiment performed on **13** showed a cross peak between 3-H and 7-H. This demonstrated that the 7-OH group points away from the C-3 in the other bridge. Moreover, the coupling constants $J_{6,7}$ = 6.6 and $J_{7,8}$ = 9.6 Hz in the ^{1}H-NMR spectrum support the relative configuration assigned to C6–C8 and are consistent with the conformation[10] shown for **13**.

Our main goal was the transformation of **12** into the dione **9**. The ready acid-catalyzed bicyclization of **8** to **13** foreshadowed that acidic conditions in the oxidation of **12** would lead to products derived from **13**. In fact, the Jones oxidation of **12** resulted in 96% of the bicyclic ketone **15**.

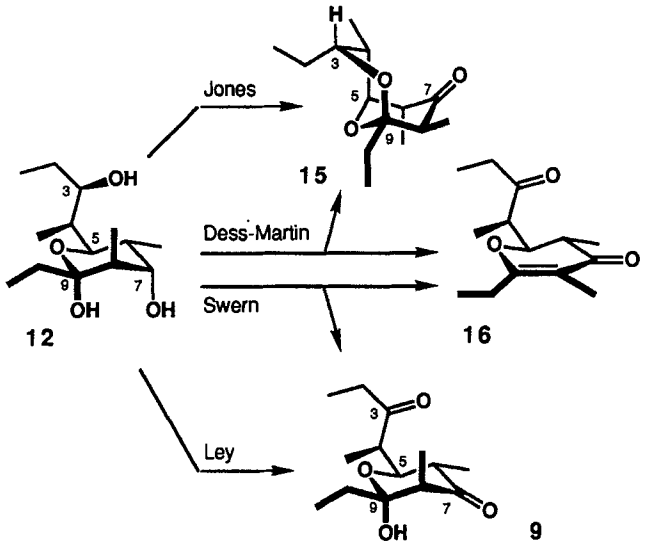
Clearly, acidic oxidation methods are counterindicated. The Dess-Martin oxidation[11] at nearly neutral pH resulted in **15** and the dihydropyrone **16**. The Swern oxidation again led to the undesired elimination product **16** (51%). However, NMR spectra also indicated the formation of small amounts (34%) of the desired **9**. Likewise, NMR spectra revealed the predominant formation of the desired **9** in the Ley oxidation[12] of **12** on a small scale. While these experiments were at least encouraging, progress along these lines was slow, so that alternate ways were explored.

The C-5-Protected Intermediate 22

A less concise, but still viable approach to the hydroxy triketone **4** is to proceed via a 7,9-diketone and to forfeit

the correct configuration at C-8. This appeared tolerable, inasmuch as **17** with the undesired configuration at C-8 should not cyclize to a trioxaadamantane **18**, because of severe 1,3-diaxial interactions between the methyl groups at C-6 and C-8 in **18**.

Scheme 5



Therefore, the intermediate **9** with the correct configuration at C-8 should cyclize to **5** by starting from diketone **4** and its C-8 epimer, whereas under the same conditions the C-8 epimer **17** should by default equilibrate at C-8 and eventually also cyclize to the desired trioxaadamantane **5**. Nevertheless, the approach via a 7,9-diketone such as **19** is still fraught with the potential pyranose formation between the C-3 hydroxyl and the C-7 carbonyl groups. Protection of the latter is therefore needed before the 3-hydroxyl function is liberated. This led to the protocol in Scheme 7.

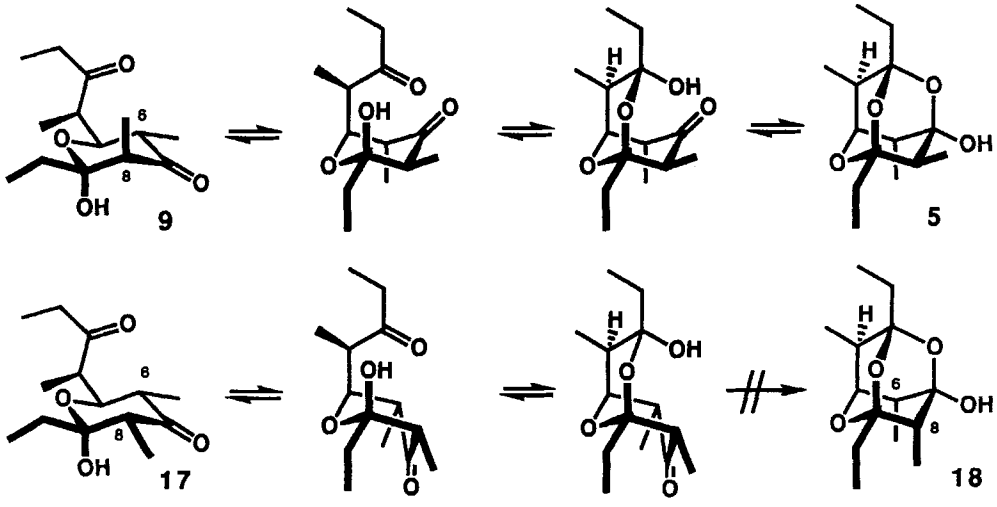
The C-7 alcohol function in **11** was oxidized with the Dess-Martin reagent[11] in pyridine to the β-diketone **19** in 96% yield. The resulting β-diketone moiety was protected as the diethylboryl derivative **20** (65%) according to the procedure of Köster[13]. Compound **20** was directly subjected to the Jones oxidation, because we anticipated that the 3-trimethylsilyloxy group would be hydrolyzed under the acidic reaction conditions. In fact, the ketone **21** was obtained in 92% yield. At this stage the desired triketone **22** could be obtained either as indicated by Köster[14] by refluxing **21** in methanol or simply by treating **21** with HF in pyridine at room temperature (84% yield).

The success of the "quasi direct" Jones oxidation of a trimethylsilyl ether led our attention to other direct oxidation methods of trimethylsilyl ethers[15]. For instance, the Swern oxidation of trimethylsilyl ethers had been reported previously[16]. Much to our delight, the Swern oxidation of **11** provided direct access to **22** in 68% yield, effectively differentiating between the trimethylsilyl and the *tert*-butyldimethylsilyl groups[17]. It is noteworthy that a δ-hydroxy ketone is not an intermediate in this transformation. Probably, **11** is transformed first into a 3,7-bis(oxysulfurane) from which the carbonyl functions are generated by subsequent addition of a base. This route therefore allowed a rapid access to the cyclization precursor **22**. The triketone formed is present as a mixture of C-8 epimers and the corresponding enols.

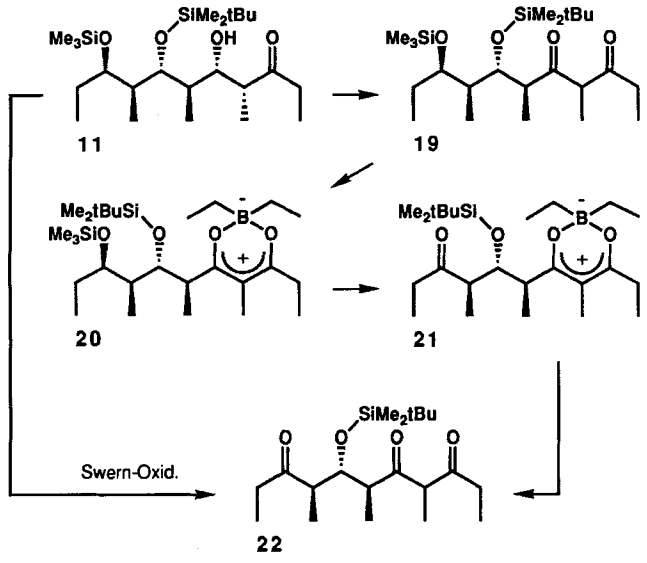
Tricyclization of the Hydroxy Triketone 4 to the Trioxaadamantane 5

Removal of the TBDMS group in **22** was now required in order to liberate the hydroxy triketone **4** and to initiate the tricyclization reaction. Treatment of **22** with HF in acetonitrile led to a quantitative conversion into the dihydropyrone **16**. This observation suggested that deprotection of **22** was followed by monocyclization of the hydroxy triketone **4** to the tetrahydropyrone **9**, and that the undesired elimination of water from **9** to form the dihydropyrone **16** was rapid under such acidic conditions, as observed in similar systems by Albizati[18].

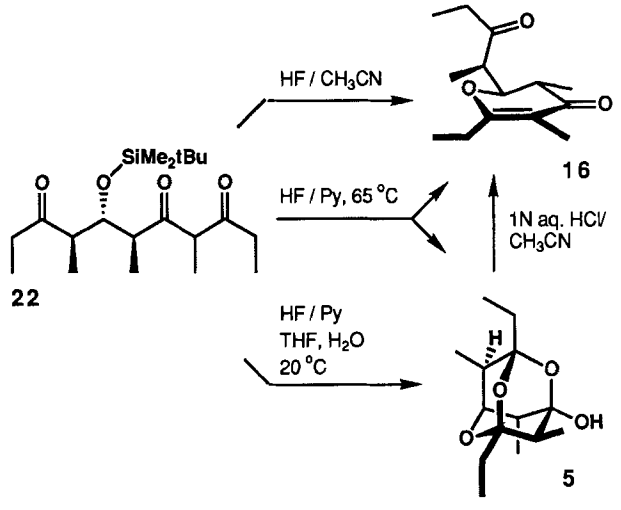
Scheme 6



Scheme 7



Scheme 8



Therefore, the deprotection of **22** was attempted with the less acidic HF/pyridine system at 65°C. This led for the first time to the desired trioxaadamantane **5** in 60% yield accompanied by 37% of the worthless dihydropyrone **16**. If the removal of the TBDMS group could be facilitated somehow, application of the correspondingly milder conditions should allow the formation of higher proportions of **5**. To this end, the deprotection was carried out in the presence of catalytic amounts of water at room temperature providing **5** in 72% yield, free of **16**. It is no surprise that the trioxaadamantane **5** itself is also sensitive to acidic conditions: Treatment of **5** with 1 N aqueous HCl/CH_3CN (1:4) resulted in immediate and quantitative formation of **16**.

The fact that the yield of **5** exceeded 50% on tricyclization of **22** indicates that both C-8 epimers of **4** cyclized as anticipated to the desired isomer of **5**. Thus, this model study delineated a route to the trioxaadamantane nucleus of muamvatin, a route which we have used successfully in establishing the absolute configuration of muamvatin[3].

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Experimental

All temperatures quoted are not corrected. – ^1H, ^{13}C NMR: Bruker AC-300. – Boiling range of petroleum ether: 40–60°C. – Flash chromatography: Kieselgel 60 (0.040–0.063 mm, Merck, Darmstadt).

1. *(4R*,5S*,6R*,7R*,8S*,9R*)-7-(tert-Butyldimethylsilyloxy)-5-hydroxy-4,6,8-trimethyl-9-(trimethylsilyloxy)undecan-3-one* (**11**): 5.0 ml (2.5 mmol) of a 0.5 M solution of 9-BBN triflate was added at −78°C dropwise to a solution of 215 mg (2.5 mmol) of 3-pentanone and 0.48 ml (2.8 mmol) of ethyldiisopropylamine in 10 ml of ether, resulting in the formation of a white precipitate. The mixture was stirred for 1 h at 0°C and then cooled again to −78°C. A solution of 593 mg (1.64 mmol) of (*2R*,3R*,4R*,5S**)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-5-(trimethylsilyloxy)heptanal (**10**)[1] in 3 ml of ether was added dropwise. The mixture was allowed to reach room temp. during 12 h. Then 10 ml of a pH 7 phosphate buffer was added, and the mixture was extracted five times with 50 ml each of ether. The combined organic phases were concentrated, and the residue was taken up in 6 ml of methanol. At 0°C 3 ml of 30% aqueous H_2O_2 was added dropwise. After stirring for 2 h at room temp. 10 ml of water was added, and the mixture was extracted five times with 50 ml each of ether. The combined organic phases were washed with 20 ml of brine, dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography with ether/petroleum ether (1:10) to give 627 mg (85%) of **11** as a colorless oil. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 3H), 0.12 (s, 3H), 0.10 (s, 9H), 0.89 (s, 9H), 0.83–0.91 (m, 9H), 1.04 (t, *J* = 7.3 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.40–1.52 (m, 1H), 1.52–1.65 (m, 1H), 1.66–1.80 (m, 1H), 1.87–2.00 (m, 1H), 2.40–2.62 (m, 3H), 3.50 (t, *J* = 0.6 Hz, 1H, OH), 3.60 (m, 1H), 3.79 (dd, *J* = 5.0 and 4.1 Hz, 1H), 3.99 (ddd, *J* = 9.9, 2.2, and 2.2 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.4, −4.3, 1.0 (3 C), 7.9, 8.0, 10.3, 10.4, 16.1, 18.1, 25.9, 28.4, 33.6, 37.7, 43.9, 48.3, 73.2, 74.9, 79.3, 214.1. – $C_{23}H_{50}O_4Si_2$ (446.8): calcd. C 61.83, H 11.28; found C 61.89, H 11.17.

2. *(3R*,4S*,5R*,6S*,1'S*,2'R*)-2-Ethyltetrahydro-6-(2-hydroxy-1-methylbutyl)-3,5-dimethyl-2H-pyran-2,4-diol* (**12**): To a solution of 232 mg (0.52 mmol) of **11** in 2 ml of THF was added 1.5 ml (1.5 mmol) of a 1 M solution of tetrabutylammonium fluoride in THF. After stirring for 90 min TLC showed complete consumption of **11**. The solvent was removed in vacuo, and the residue was taken up in 30 ml of ether. The solution was washed with 10 ml of brine, and the aqueous phase was extracted three times with 40 ml of ether. The combined organic phases were washed with 30 ml of a saturated aqueous NH_4Cl solution, which induced pyranol formation, dried with $MgSO_4$, and concentrated. The residue was purified by flash chromatography with ether/petroleum ether (1:2) to give 124 mg (92%) of **12** as colorless crystals. Recrystallization from ether/petroleum ether furnished a material of m.p. 110–114°C. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.93 (m, 12H), 1.01 (d, *J* = 7.1 Hz, 3H), 1.27–1.41 (m, 1H), 1.45–1.63 (m, 3H), 1.67–1.77 (m, 1H), 1.93–2.08 (m, 2H), 3.65 (broad s, 1H), 3.73 (s, 1H, OH), 3.83–3.91 (m, 2H), 4.03 (broad d, *J* = 6 Hz, 1H, OH), 5.17 (s, 1H, OH). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 6.6, 10.4, 10.7, 13.5, 13.7, 27.2, 30.4, 31.7, 34.7, 39.4, 72.0, 75.6, 76.4, 100.3. – $C_{14}H_{28}O_4$ (260.4): calcd. C 64.58, H 10.84; found C 64.68, H 10.70.

3. *(1R*,3S*,4R*,5S*,6R*,7S*,8S*)-1,3-Diethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-ol* (**13**) *and (1R*,3S*,4S*,5R*,8S*)-*

1,3-Diethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-6-ene (**14**): To a solution of 122 mg (0.46 mmol) of the tetrahydropyranol **12** in 10 ml of methanol was added ca. 10 mg of *p*-toluenesulfonic acid. After stirring for 1 h the solvent was removed in vacuo, and the residue was purified by flash chromatography with ether/petroleum ether (1:2) to give 78 mg (69%) of **13** and 24 mg (23%) of **14**.

13: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.20–1.40 (m, 2H), 1.40–1.56 (m, 3H), 1.56–1.72 (m, 1H), 1.72–1.83 (m, 1H), 2.07 (m, 1H), 3.67 (s, 1H), 3.85 (ddd, *J* = 7.8, 5.3, and 3.9 Hz, 1H), 4.30 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.3, 10.0, 12.4, 13.7 (2 C), 26.6, 32.5, 34.7, 38.4, 41.5, 72.3, 73.7, 81.1, 100.1. – $C_{14}H_{26}O_3$ (242.4): calcd. C 69.38, H 10.81; found C 69.33, H 10.86.

14: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81 (t, *J* = 7.4 Hz, 3H), 0.91 (d, *J* = 7.4 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.24–1.40 (m, 2H), 1.40–1.54 (m, 1H), 1.57 (t, *J* = 1.6 Hz, 3H), 1.62–1.73 (m, 2H), 1.95 (m, 1H), 3.59 (s, 1H), 3.86 (ddd, *J* = 7.8, 6.1, and 3.0 Hz, 1H), 5.71 (m, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.1, 9.8, 12.8, 18.1, 20.6, 25.3, 29.7, 34.9, 36.5, 70.8, 80.0, 97.6, 130.37, 130.41. – $C_{14}H_{24}O_2$ (224.3): calcd. C 74.95, H 10.78; found C 74.84, H 10.59.

4. *(1R*,3S*,4R*,5R*,6R*,8S*)-1,3-Diethyl-4,6,8-trimethyl-2,9-dioxabicyclo[3.3.1]nonan-7-one* (**15**): The Jones reagent was prepared from 6.68 g (66.8 mmol) of chromium trioxide, 20 ml of water, and 5.6 ml of conc. sulfuric acid. To a solution of 27.3 mg (0.10 mmol) of the tetrahydropyranol **12** in 5 ml of acetone was added at 0°C ca. 10 drops of the Jones reagent until the greenish flaky precipitate coagulated. After stirring for 10 min at 0°C 0.5 ml of 2-propanol was added, and stirring was continued for 10 min. Then 30 ml of brine was added, and the mixture was extracted three times with 40 ml each of ether. The combined organic phases were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with ether/petroleum ether (1:10) furnished 22.8 mg (96%) of the ketone **15** as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80 (d, *J* = 7.4 Hz, 3H), 0.97 (d, *J* = 7.4 Hz, 3H), 1.05 (d, *J* = ca. 7 Hz, 3H), 1.08 (d, *J* = ca. 7 Hz, 3H), 1.14–1.51 (m, 3H), 1.32 (d, *J* = 7.4 Hz, 3H), 1.51–1.66 (m, 1H), 1.74–1.84 (m, 1H), 2.46 (q, *J* = 7.4 Hz, 1H), 2.53 (q, *J* = 6.8 Hz, 1H), 3.36 (ddd, *J* = 7.8, 5.0, and 2.7 Hz, 1H), 3.84 (broad s, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.0, 8.2, 9.6, 12.3, 19.0, 25.8, 31.9, 35.4, 47.0, 48.6, 70.7, 81.0, 102.5, 212.6. – $C_{14}H_{24}O_3$ (240.3): calcd. C 69.96, H 10.06; found C 69.86, H 10.15.

5. *(6R*,7R*,8R*,9S*)-7-(tert-Butyldimethylsilyloxy)-4,6,8-trimethyl-9-(trimethylsilyloxy)-3,5-undecanedione* (**19**): To a solution of 52 mg (0.12 mmol) of **11** in 10 ml of CH_2Cl_2 were added 100 mg of powdered molecular sieves (A 4) and 94 µl (1.2 mmol) of pyridine. After stirring for 1 h at room temp. the mixture was cooled to −5°C. Then 49 mg and, after 1 h, once more 10 mg (in total 0.14 mmol) of the Dess-Martin reagent[11] were added. After continuous stirring for 1 h TLC showed complete consumption of **11**. The solution was added to a mixture of 20 ml of ether, 10 ml of a semisaturated aqueous $NaHCO_3$ solution, and 110 mg (1.2 mmol) of $Na_2S_2O_3$. The phases were separated after stirring for 2 h. The aqueous phase was extracted three times with 40 ml each of ether. The combined organic extracts were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with ether/petroleum ether (1:20) furnished 51 mg (99%) of **19** as a colorless oil. The product was a mixture of two epimieric diketones and the enol. The enol showed ^{13}C-NMR signals for C-3, C-4, and C-5 at 194.3, 104.2, and 195.7, respectively. The corresponding signals in the diketone were observed at 208.3, 60.7, and 208.6, respectively. The second diketone was detected by a C-4 signal at δ = 59.5. – $C_{23}H_{48}O_4Si_2$ (444.8): calcd. C 62.11, H 10.88; found C 61.76, H 10.74.

6. *(6R*,7R*,8S*)-7-(tert-Butyldimethylsilyloxy)-4,6,8-trimethylundecane-3,5,9-trione* (**22**)

a) *Via the Diethylboryl Intermediates* **20** *and* **21**: To a solution of 180 mg (0.40 mmol) of the diketone **19** in 5 ml of hexane was added 1.0 ml (1.0 mmol) of a 1 M solution of triethylborane in hexane. After the addition of ca. 20 mg of pivalic acid the mixture was refluxed for 5 h. The solvent was removed in vacuo, and the residue was purified by chromatography with ether/petroleum ether (1:5) to give 134 mg (65%) of the diethylboryl derivative **20** as a yellow oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.03 (s, 3H), 0.05 (s, 3H), 0.25–0.35 (m, 2H), 0.43–0.53 (m, 2H), 0.69 (t, *J* = 7.7 Hz, 3H), 0.84 (s, 9H), 0.77–0.95 (m, 6H), 0.81 (s, 9H), 0.97 (d, *J* = ca. 7.4 Hz, 3H), 1.00 (d, *J* = ca. 7.4 Hz, 3H), 1.10 (t, *J* = 7.4 Hz, 4H), 1.40–1.53 (m, 1H), 1.63–1.83 (m, 2H), 1.82 (s, 3H), 2.37 (m, 2H), 3.00 (dq, *J* = 8.3 and 7.0 Hz, 1H), 3.64 (ddd, *J* = 8.2, 6.5, and 4.5 Hz, 1H), 4.04 (dd, *J* = 8.3 and 3.0 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.7, −4.2, 0.9 (3 C), 8.6, 8.8, 9.1, 9.6, 11.4, 11.7, 14.2, 18.1, 25.9 (3 C), 28.3, 29.0, 42.2, 44.8, 75.0, 75.2, 104.3, 192.4, 193.0, and two broad signals at δ ca. 10.0 and 12.5.

134 mg (0.26 mmol) of **20** obtained above was dissolved in 10 ml of acetone and oxidized with the Jones reagent as described under 4. to give 105 mg (92%) of the crude ketone **21**, which could be purified by filtration over neutral Al_2O_3 with ether/petroleum ether (1:10). Flash chromatography over silica gel led to decomposition. Likewise, the solution in $CDCl_3$ was not stable. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3H), 0.04 (s, 3H), 0.24–0.34 (m, 2H), 0.41–0.54 (m, 2H), 0.68 (t, *J* = 7.8 Hz, 3H), 0.84 (s, 9H), 0.79–0.88 and 0.88–0.94 and 1.01–1.18 (m, 15H), 1.84 (s, 3H), 2.30–2.63 (m, 4H), 2.67–2.82 (m, 1H), 3.00 (m, 1H), 4.40 (m, 1H).

A ca. 4 M solution of HF/pyridine was prepared from 2.1 g of 70% HF/pyridine, 6 ml of pyridine, and 10 ml of THF. 1.5 ml of this solution was added to a solution of 55 mg (0.12 mmol) of the crude diethylboryl compound **21** in 3 ml of THF. Stirring overnight led to decolorization. The solution was concentrated, and the residue was purified by flash chromatography with ether/petroleum ether (1:4) to give 39 mg (84%) of **22** showing the same spectral data as the material obtained below.

b) *By Oxidation of the Silyl Ether* **11**: To a solution of 2.6 ml (30 mmol) of oxalyl chloride in 50 ml of CH_2Cl_2 was added at −78°C a solution of 4.3 ml (60 mmol) of dimethyl sulfoxide in 20 ml of CH_2Cl_2. After stirring for 15 min a solution of 1.00 g (2.24 mmol) of **11** in 10 ml of CH_2Cl_2 was added dropwise. Stirring was continued for 2 h at −78°C. The mixture was then allowed to reach −30°C over a period of 45 min. Then 14 ml (100 mmol) of triethylamine was added dropwise. The mixture was allowed to reach 0°C. Subsequently 20 ml of a saturated aqueous NH_4Cl solution and 200 ml of ether were added. Enough water was added to dissolve the precipitate formed. The phases were separated, and the aqueous phase was extracted four times with 100 ml each of ether. The combined organic phases were washed with 50 ml of brine, dried with $MgSO_4$ and concentrated. The residue was purified by flash chromatography with ether/petroleum ether (1:20 followed by 1:10 and 1:4). Thus 566 mg (68%) of **22** was obtained as a mixture of epimeric triketones and the enol. The following characteristic signals in the ^{13}C-NMR (75 MHz, $CDCl_3$) spectrum could be recorded. Enol: δ = 17.8, 25.6, 29.7, 34.8, 41.7, 51.7, 75.0, 104.3, 192.3, 196.2, 211.6; triketone 1: 34.1, 35.7, 50.5, 50.8, 60.2, 74.5, 207.9, 211.8; triketone 2: 34.6, 35.6, 49.4, 50.9, 59.4, 74.0, 206.9, 208.4, 212.0.

– $C_{20}H_{38}O_4Si$ (370.6): calcd. C 64.82, H 10.33; found C 64.80, H 10.30.

7. *(2R*,3R*,1'S*)-6-Ethyl-2,3-dihydro-3,5-dimethyl-2-(1-methyl-2-oxobutyl)-4H-pyran-4-one* (**16**): To a solution of 70 mg (0.19 mmol) of the triketone **22** in 1.5 ml of acetonitrile was added 1 ml of a solution prepared by mixing 5 ml of 40% aqueous HF with 45 ml of acetonitrile. After stirring for 12 h TLC indicated complete consumption of the starting material. 10 ml of a saturated aqueous NH_4Cl solution was added, and the mixture was extracted three times with 20 ml each of ether. The combined extracts were dried with $MgSO_4$ and concentrated. Flash chromatography of the residue with ether/petroleum ether (1:4) furnished 45 mg (100%) of **16** as a colorless liquid. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.01 (t, *J* = 7.3 Hz, 3H), 1.05 (t, *J* = 7.6 Hz, 3H), 1.13 (d, *J* ca. 7 Hz, 3H), 1.15 (d, *J* ca. 7 Hz, 3H), 1.69 (s, 3H), 2.18–2.61 (m, 5H), 2.95 (dq, *J* = 7.0 and 7.0 Hz, 1H), 4.23 (dd, *J* = 7.9 and 6.7 Hz, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 7.5, 9.1, 10.7, 13.31, 13.39, 25.5, 34.9, 40.9, 47.3, 83.8, 107.9, 171.1, 194.7, 211.5. – $C_{14}H_{22}O_3$ (238.3): calcd. C 70.56, H 9.30; found C 70.58, H 9.56.

8. *(1R*,3R*,5R*,7R*,8S*,9R*,10R*)-3,5-Diethyl-8,9,10-trimethyl-2,4,6-trioxatricyclo[3.3.1.1^{3,7}]decan-1-ol* (**5**): 1.0 ml of the HF/pyridine solution prepared as described under 5. and 106 mg (0.29 mmol) of the triketone **22** were kept in a polyethylene bottle at room temp. After 4 h TLC indicated no change. Therefore, one drop of water was added. Since TLC indicated a partial reaction after 1 d, 1 ml of the above HF/pyridin solution was added after 3 d. After a total time of 4 d TLC revealed complete consumption of the starting material. The solution was added into 100 ml of ether and 50 ml of a semisaturated aqueous NH_4Cl solution. The phases were separated, and the aqueous phase was extracted three times with 50 ml each of ether. The combined organic phases were washed with 50 ml of brine, dried with $MgSO_4$, and concentrated. Flash chromatography of the residue with ether/petroleum ether (1:2) furnished 53 mg (72%) of the trioxaadamantane **5** as a colorless oil, which slowly crystallized. Recrystallization from petroleum ether furnished a material which melted in the range 87–95°C. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88–0.98 (m, 9H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 1.40–1.74 (m, 5H), 1.80–1.94 (m, 2H), 2.82–2.83 (broad m, 1H, OH), 3.74 (broad s, 1H). – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 5.8, 6.0, 7.1, 13.2, 13.5, 29.7, 29.9, 35.7, 37.5, 43.2, 78.7, 97.5, 101.9, 102.3. – $C_{14}H_{24}O_4$ (256.3): calcd. C 65.60, H 9.44; found C 65.49, H 9.60.

[1] Part XLV: R. W. Hoffmann, G. Dahmann, M. W. Andersen, *Synthesis*, submitted.
[2] D. M. Roll, J. E. Biskupiak, C. L. Mayne, C. M. Ireland, *J. Am. Chem. Soc.* **1986**, *108*, 6680–6682.
[3] R. W. Hoffmann, G. Dahmann, *Tetrahedron Lett.* **1993**, *34*, 1115–1118.
[4] I. Paterson, M. V. Perkins, *J. Am. Chem. Soc.* **1993**, *115*, 1608–1610.
[5] H. Agback, Kabi Pharmacia AB, Uppsala, Sweden, personal communication, **1991**.
[6] R. W. Hoffmann, *Angew. Chem.* **1987**, *99*, 503–517; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 489–503.
[7] [7a] W. Fenzl, R. Köster, H. J. Zimmermann, *Liebigs Ann. Chem.* **1975**, 2201–2210. – [7b] S. Masamune, S. Mori, D. VanHorn, D. W. Brooks, *Tetrahedron Lett.* **1979**, 1665–1668. – [7c] D. A. Evans, J. V. Nelson, E. Vogel, T. R. Taber, *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111. – [7d] D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, *13*, 1–115.
[8] T. Inoue, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174–178.
[9] [9a] D. V. Patel, F. VanMiddlesworth, J. Donaubauer, P. Gannett, C. J. Sih, *J. Am. Chem. Soc.* **1986**, *108*, 4603–4614. – [9b] M. W. Andersen, S. Hildebrandt, G. Dahmann, R. W. Hoffmann, *Chem. Ber.* **1991**, *124*, 2127–2139. – [9c] W. R. Roush, *J. Org. Chem.* **1991**, *56*, 4151–4157.
[10] For conformational aspects of this system see: N. S. Zefirov, V. A. Palyulin, *Top. Stereochem.* **1991**, *20*, 171–230.
[11] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
[12] [12a] W. P. Griffith, S. V. Ley, G. P. Whitcombe, A. D. White, *J. Chem. Soc., Chem. Commun.* **1987**, 1625–1627. – [12b] W. P. Griffith, S. V. Ley, *Aldrichim. Acta* **1990**, *23*, 13–19.
[13] R. Köster, G. W. Rotermund, *Liebigs Ann. Chem.* **1965**, *689*, 40–64.
[14] W. V. Dahlhoff, W. Schüßler, R. Köster, *Liebigs Ann. Chem.* **1976**, 387–394.
[15] J. Muzart, *Synthesis* **1993**, 11–27.
[16] [16a] G. A. Tolstikov, M. S. Miftakhov, M. E. Adler, N. G. Komissarova, O. M. Kuznetsov, N. S. Vostrikov, *Synthesis* **1989**, 940–942. – [16b] C. M. Afonso, M.T. Barros, C. D. Maycock, *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1221–1223.
[17] G. A. Tolstikov, M. S. Miftakhov, N. S. Vostrikov, N. G. Komissarova, M. E. Adler, O. M. Kuznetsov, *Zh. Org. Khim.* **1988**, *24*, 224–225.
[18] U. N. Sundram, K. F. Albizati, *Tetrahedron Lett.* **1992**, *33*, 437–440.

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