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Synthesis of Bridged Nine-membered Ring Ethers: Studies Directed towards the Synthesis of Eunicellin-based Marine Diterpenes

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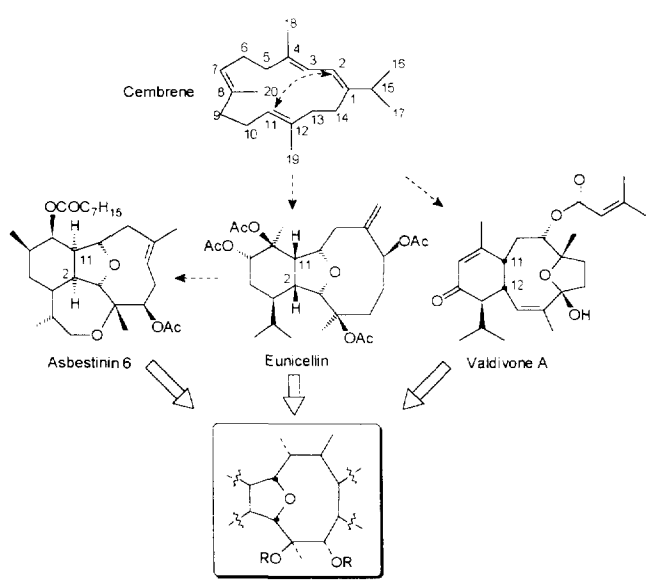
Abstract: A concise annulation-fragmentation strategy has been elaborated for the construction of the bridged nine-membered ring ether moiety of the eunicelline diterpenes. Key steps are a SmI_2-induced Barbier cyclization and an oxidative ring fission using cerium(IV) ammonium nitrate (CAN). © 1997 Elsevier Science Ltd.

Soft corals and gorgonian octocorals offer a rich source of diterpene metabolites.[1] Besides the extensive structural class of macro and monocyclic cembranes,[2] polycyclic diterpenes termed eunicellins,[3] asbestinins[4] and valdivones[5] have also been isolated from these marine organisms and a biogenetic route[4a, 6] to these oxy-

Scheme 1

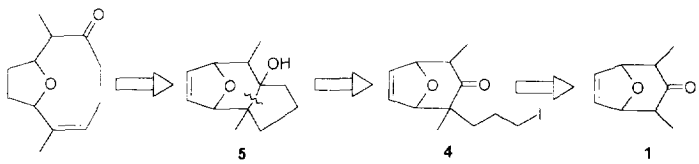


genated metabolites has been proposed (Scheme 1). Their structural and stereochemical complexity combined with a wide range of cytotoxic, antiproliferative and antiinflammatory bioactivities[1b, 7] have attracted the interest of natural products chemists. The oxabicyclic core common to the three polycyclic classes is an α,α′-bridged nine-membered ring ether.

The need for synthetic approaches[8] to eunicellin-based diterpenes together with the challenge of the synthesis of strained medium sized rings[9, 10] have prompted us to develop a concise sequence for the construction of the bridged nine-membered ring ether skeleton, which is also an oxygen-bridged 10-membered carbocycle.

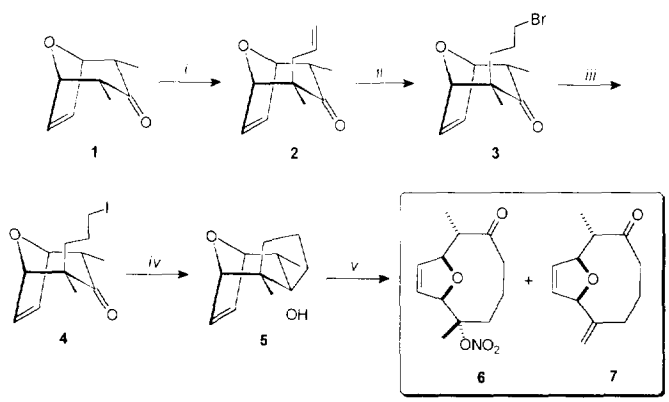
The methodology developed for the synthesis of medium ring ethers falls into two categories.[11] Direct cyclization of acyclic precursors[12] and ring enlargement achieved by fragmentation[13] or rearrangement.[14] Scheme 2 illustrates our retrosynthetic plan which is based on a ring enlargement strategy and involves oxidative scission of tricyclic alcohol **5** which in turn is obtained from bicyclic ketone **1** *via* annulation of a five-membered ring.

Scheme 2



The synthetic route is outlined in Scheme 3.

Scheme 3



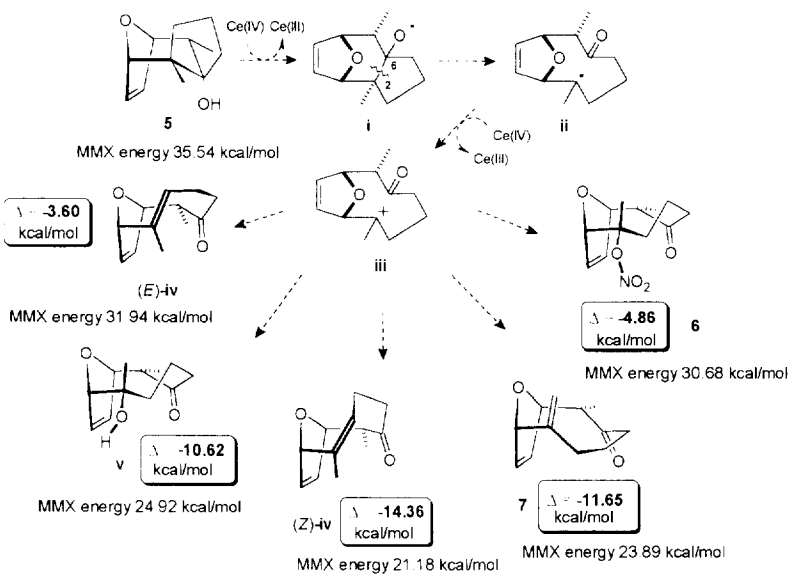
Reagents and conditions: *(i)* LDA, allyl bromide, THF, -20 °C, 85%; *(ii)* $HBr_{(g)}$, hv, hexane, 60 °C, 53%; *(iii)* NaI, $(CH_3)_2CO$, r.t., 82%, *(iv)* SmI_2, THF, -78 °C o.n. to r.t., 88%; *(v)* $Ce(NH_4)_2(NO_3)_6$, CH_3CN/H_2O (1:2), 85 °C (5 min) then 0 °C, 27% of **6**, 7% of **7**, 14% of educt **5**.

To circumvent problems concerning regioselectivity, we used σ-symmetric ketone 2α,4α-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one[15] (**1**) as starting material. The two methyl groups of **1** also facilitated the interpretation of NMR spectra. Subsequent allylation of bicylic ketone **1** gave racemic oxabicycle **2** with 100%

axial diastereoselectivity due to the convex-concave principle.[16] Furthermore, no diallylated sideproduct was formed in the course of this reaction.[17] The terminal olefinic bond of **2** was hydrobrominated chemoselectively and regioselectively in the anti-Markovnikov sense (dry HBr gas under irradiation with a medium pressure Hg-vapor lamp), and in a Finkelstein reaction bromine was exchanged for iodine (**3** → **4**) in a straightforward manner. With ω-iodo ketone **4** in hand the way was smoothed for the SmI_2-induced Barbier-like cyclization,[18, 19] which provided *cis*-fused tricyclic, tertiary alcohol **5** in excellent chemical yield and, as expected, with complete retention of stereochemistry at the quaternary centre C(2).[20] The strained tricyclic alcohol **5** was finally cleaved oxidatively using cerium(IV) ammonium nitrate (CAN)[18, 21] as powerful one electron oxidant. Novel major product **6** and also minor ketodiolefin **7** represent the desired bicyclic framework.

In view of CAN-mediated fragmentation reactions described in the literature[21] we expected primarily *endo*-olefinic derivatives (*Z*)- and (*E*)-***iv*** and also tertiary alcohol ***v*** as probable fragmentation products (Scheme 4). Formation of the nitrato substituted nine-membered ring ether **6** as well as the *exo*-methylene substituted minor component **7** were unexpected at first sight. Hence we were prompted to perform MMX calculations[22] in order to discuss the possible mechanism and to obtain information about the thermodynamic and stereochemical course.[23]

Scheme 4



Mechanistically, the CAN-mediated fragmentation is assumed to involve single electron transfer (SET) from the free hydroxy group of tertiary alcohol **5** to highly oxidized cerium (IV) ion, giving rise to unstable oxygen radical intermediate ***i*** and a stable cerium (III) ion. Radical ***i*** is stabilized by homolytic cleavage of the

fully substituted C(2)-C(6)-bond, providing tertiary alkyl radical intermediate ***ii***. Since CAN is present in a 2.5-fold excess, the radical mechanism can switch efficiently to an ionic path giving tertiary cation ***iii*** after renewed SET to a second cerium(IV) ion. Possible termination reactions of tertiary carbonium ion ***iii*** are: (1) Elimination and formation of *endo*-oriented olefins (*Z*)-***iv*** and (*E*)-***iv***, (2) Trapping with water molecules to generate tertiary alcohol ***v***, (3) **E1** reaction and formation of *exo*-methylene substituted olefin **7**, and (4) Nucleophilic collapse with nitrate anion to provide major oxabicycle **6**.

A comparison of calculated MMX energies of tricyclic educt **5** and the set of structurally related termination products **6** , **7** , ***iv*** and ***v*** shows the four termination pathways to proceed energetically downhill. Hypothetical (*Z*)-configurated *endo*-olefin (*Z*)-***iv*** shows the largest decrease of MMX energy (−14.36 kcal/mol), followed by isolated *exo*-methylene substituted nine-membered ring **7** (−11.65 kcal/mol). **E1**-like formation of the *exo*cyclic double bond in **7** instead of trisubstituted *endo*-olefin (*Z*)-***iv*** is assumed to be preferred on general stereoelectronic grounds. The significantly larger decrease of MMX energy calculated for minor keto diolefin **7** and hypothetical tertiary alcohol ***v*** (−10.62 kcal/mol) than for major ester **6** (−4.86 kcal/mol) suggests that **6** is formed under kinetic control.

With respect to calculated 3D structures it appears that the low MMX energy of minor ring ether **7** minimizes transannular repulsion and eclipsing interactions.

In conclusion, starting from readily available oxabicyclic ketone **1** we have elaborated a concise strategy (5 steps, 13% overall yield) for the construction of the α,α′-bridged nine-membered ring ether framework present in eunicellin-based diterpenes. As a key step the SmI_2-induced Barbier cyclization has been successfully applied to an unsaturated oxabicylic ω-iodo ketone generating a strained tricyclic alcohol with high efficiency. This reaction was carried out on a gram scale and under extremely mild conditions (−78 °C to r.t.). The final CAN-mediated ring scission provided unexpected and novel nine-membered ring ethers. Nitrate ester **6** and *exo*cyclic, disubstituted olefin **7** are formed, while trisubstituted, *endo*cyclic olefin (*Z*)-***iv*** was not detected.

EXPERIMENTAL

General Remarks. Melting points: Büchi apparatus. – Infrared spectra: Perkin–Elmer FT 1710. – ^{1}H NMR spectra: Bruker WH 90, WP 200 SY or AM 300 spectrometer, solvent $CDCl_3$ unless otherwise stated. – ^{13}C NMR spectra: Bruker WP 200 SY or a Bruker AM 300. APT (attached proton test): spin echo-based selection of multiplicities of ^{13}C signals. Quaternary C and CH_2 carbon atoms give positive signals (+), while CH and CH_3 give negative signals (−). – Elemental analysis (EA): Heraeus CHN-Rapid. – UV/VIS spectrum: Beckman Spectrophotometer 3600. – Preparative column chromatography was performed on J. T. Baker silica gel (particle size 30-60 μm). – Analytical t.l.c. was carried out on aluminum-backed 0.2-mm silica gel 60 F_{254} plates (E. Merck). – E (ethyl ether). PE (light petroleum, bp 40 - 60°C).

α-Allylation of 2α,4α-Dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**1**). A predried 500 mL two-necked flask equipped with a gas inlet and a septum was heated under a weak stream of nitrogen. THF (175 mL) and diisopropylamine (14.45 mL, 103 mmol) were added and the solution was cooled to 0 °C. A 1.6 M solution of n-butyllithium in hexane (62.10 mL, 99 mmol) was added dropwise. The mixture was stirred for 15 min and then cooled to –20 °C. Oxabicycle **1** (13.68 g, 90 mmol) was dissolved in THF (75 mL) and then added dropwise. After stirring at –5 °C for 1 h, the solution was recooled to –20 °C and allyl bromide (54.45 g, 450 mmol) was added. The mixture was stirred for 20 min and then worked up by washing with water (5 × 200 mL). The aqueous phase was reextracted with ether (2 × 300 mL) and the combined organic phase was dried ($MgSO_4$) and concentrated on a rotary evaporator. The resulting yellow solid was purified by column chromatography (PE/E, 2:1) to yield 14.79 g (85%) of **2** as a pale yellow solid. mp 37 °C; IR (KBr) ν 3087, 2966, 1708, 1461, 1377, 1043, 921, 728 cm^{-1}; ^{1}H NMR δ 0.92 (s, 3 H, $CH_{3,eq}$), 0.96 (d, J = 7 Hz, 3 H, $CH_{3,eq}$), 2.53 (m, 2 H, CH_2), 2.93 (dq, J = 7/4 Hz, 1 H, CH_{ax}), 4.58 (d, J = 1 Hz, 1 H, *H*COR), 4.81 (dd, J = 4/1 Hz, 1 H, *H*COR), 5.08 (m, 1 H, CH_2), 5.14 (m, 1 H, CH_2), 5.69 (m, 1 H, C*H*), 6.36 (m, 2 H, C*H*); ^{13}C NMR δ 10.12 (–, CH_3), 16.85 (–, CH_3), 41.34 (+, CH_2), 47.80 (–, CH), 55.08 (+, CR_4), 82.67 (–, HC*O*R), 84.60 (–, HC*O*R), 118.51 (+, CH_2), 132.92 (–, CH), 133.38 (–, CH), 134.24 (–, CH), 208.89 (+, C=O); MS *m z* 192 (M$^+$, 9), 151 (19), 124 (25), 109 (23), 96 (100), 81 (94), 68 (33), 52 (18).

Chemo- and Regioselective Hydrobromination of Olefin **2**. A 250 mL two-necked flask equipped with a gas inlet tube and a reflux condenser was charged with olefin **2** (0.77 g, 4 mmol) and dry petrolether (120 mL). Nitrogen was passed through the solution for 15 min with vigorous stirring. While the mixture was heated to reflux and irradiated with a medium pressure Hg-vapor lamp, dry HBr gas was bubbled through the solution for 4 h. Then nitrogen was passed through the ice cooled reaction mixture for 15 min, which was then washed with a saturated $Na_2S_2O_3$ solution (3 × 100 mL). The aqueous phase was reextracted with ether and the combined organic phase was dried ($MgSO_4$) and concentrated on a rotary evaporator. The resulting brown oil was purified by column chromatography (PE/E, 5:1) to yield 0.58 g (53%) of **3** as a pale yellow solid. mp 55 °C; IR (KBr) ν 3090, 2980, 2965, 1707, 1464, 1380, 1228, 1139, 1052, 938, 921, 726 cm^{-1}; ^{1}H NMR δ 0.93 (s, 3 H, $CH_{3,eq}$), 0.96 (d, J = 7 Hz, 3 H, $CH_{3,eq}$), 1.61 - 2.21 (m, 4 H, 2 × CH_2), 2.93 (dq, J = 7/4 Hz, 1 H, CH_{ax}), 3.38 (t, J = 6 Hz, 2 H, CH_2Br), 4.54 (d, J = 1 Hz, 1 H, *H*COR), 4.81 (dd, J = 4/1 Hz, 1 H, *H*COR), 6.36 (m, 2 H, 2 × C*H*); ^{13}C NMR δ 10.19 (–, CH_3), 16.87 (–, CH_3), 27.58 (+, CH_2), 33.67 (–, CH_2), 35.63 (+, CH_2Br), 48.92 (–, CH), 54.79 (–, CR_4), 82.73 + 83.14 (– –, HC*O*R), 85.24 + 85.87 (– –, HC*O*R), 133.42 (–, CH), 134.11 (–, CH), 211.00 (–, C=O); MS *m z* 274 (M$^+$, 100), 259 (9), 156 (27), 152 (9), 96 (21), 81 (21), 69 (9), 57 (8).

Iodination of ω-Bromo Ketone **3**. A 150 mL two-necked flask equipped with a gas inlet and a septum was charged with sodium iodide (5.28 g, 35 mmol) and heated under a weak stream of nitrogen. Acetone (60 mL) was added and the mixture was stirred until a clear solution resulted. ω-Bromoketone **3** (4.67 g, 17.04 mmol) was dissolved in acetone (20 mL) and added to the NaI solution. The flask was now taped with black paper in order to protect the light sensitive product. The mixture was stirred at r.t. for 2 h and worked up by careful

concentration to a third of the original volume. The resulting suspension was taken up in ether (75 mL) and washed with water, dilute $NaHSO_3$ solution and once more with water. The aqueous phase was reextracted with ether, the organic phase was dried ($MgSO_4$) and concentrated with a rotary evaporator. The resulting brown oil was purified by column chromatography (PE/E, 5:1). The column was taped with an aluminium foil. ω-Iodo ketone **4** (4.49 g, 82%) was isolated as a pale yellow solid which was stored at −18 °C and under light protection. mp 59 °C; IR (KBr) ν 3090, 2970, 2934, 1705, 1458, 1378, 1184, 1049, 938, 728 cm^{-1}; ^{1}H NMR δ 0.93 (s, 3 H, $CH_{3,eq}$), 0.96 (d, J = 7 Hz, 3 H, $CH_{3,eq}$), 1.59 - 2.25 (m, 4 H, 2 × CH_2), 2.92 (dq, J = 7/4 Hz, 1 H, CH_{ax}), 3.15 (t, J = 6 Hz, 2 H, CH_2I), 4.53 (d, J = 1 Hz, 1 H, *H*COR), 4.80 (dd, J = 4/1 Hz, 1 H, *H*COR), 6.36 (m, 2 H, 2 × C*H*); MS *m z* 320 (M$^+$, 21), 274 (7), 165 (49), 151 (24), 109 (24), 96 (100), 81 (62), 69 (72), 55 (16).

SmI_2-induced Cyclization of ω-Iodo Ketone **4**. A predried 100 mL two-necked flask equipped with a gas inlet and a septum was charged with Sm powder (5.60 g, 37.26 mmol) and heated under a stream of nitrogen. THF (20 mL) was added and the slurry was stirred and cooled to 0 °C. 1,2-Diiodo ethane (7.85 g, 28.02 mmol) was dissolved in THF (40 mL) and added to the Sm slurry. After stirring at 0 °C for 2 h a deep blue solution resulted which was cooled to −78 °C. ω-Iodo ketone **4** (4.48 g, 14.01 mmol) in THF (10 mL) was added to the SmI_2 solution and the mixture was allowed to warm to r. t. overnight and then taken up in ether (100 mL) and washed with saturated K_2CO_3 solution (2 × 100 mL). The aqueous phase was reextracted with ether (3 × 100 mL), the combined organic phase was dried (K_2CO_3/$MgSO_4$) and concentrated with a rotary evaporator. The resulting yellow crude product was purified by column chromatography (PE/E, 5:1) to yield tricyclic alcohol **5** (2.41 g, 88%) as a colourless viscous oil. IR ($CHCl_3$) ν 3585, 3449, 3013, 2943, 1603, 1459, 1378, 1100, 1055 cm^{-1}; ^{1}H NMR δ 0.89 (d, J = 7 Hz, 3 H, $CH_{3,eq}$), 0.90 (s, 3 H, $CH_{3,eq}$), 1.53 (t, J = 3 Hz, 2 H, CH_2), 1.68 (t, J = 3 Hz, 2 H, CH_2), 1.41 - 1.80 (m, 2 H, CH_2), 2.08 (dq, J = 7/4 Hz, 1 H, CH_{ax}), 4.35 (d, J = 2 Hz, 1 H, *H*COR), 4.49 (dd, J = 4/2 Hz, 1 H, *H*COR), 6.50 (m, 2 H, 2 × C*H*), ^{13}C NMR δ 10.83 (−, CH_3), 17.94 (+, CH_2), 20.60 (−, CH_3), 35.13 (+, CH_2), 37.20 (+, CH_2), 39.22 (−, CH), 45.66 (+, CR_4), 81.50 (+, CR_3OH), 82.81 (−, HCOR), 84.02 (−, HCOR), 133.28 (−, CH), 135.81 (−, CH); MS *m z* 194 (M$^+$, 18), 176 (20), 161 (31), 153 (18), 123 (43), 108 (88), 95 (100), 81 (70), 77 (24), 67 (36), 55 (46).

CAN-mediated Fragmentation of Tricyclic Alcohol **5**. A 5 mL two-necked flask equipped with a reflux condenser and a septum was charged with tricyclic alcohol **5** (194 mg, 1.00 mmol) and acetonitrile (1.4 mL) and the solution was heated to 85 °C. CAN (1.37 g, 2.50 mmol) was dissolved in dist. water (2.5 mL) and added rapidly. The colour of the mixture spontaneously turned to deep red and then immediately decolourized. After 5 min the reaction was interrupted by cooling with an ice bath and worked up by diluting with water (10 mL). The aqueous phase was extracted with dichloromethane (3 × 10 mL), the combined organic phase was dried (Na_2SO_4) and concentrated with a rotary evaporator. The crude product was purified by column chromatography (PE/E, 5:1) to yield 68 mg (27%) major ester **6** as a colourless solid, 13 mg (7%) minor olefin **7** as a yellow oil as well as 27 mg (14%) educt **5**. *Data for* **6**: mp 60 °C; IR (KBr) ν 2988, 2936, 2868, 1708,

1624, 1464, 1380, 1288, 1132, 860, 620 cm^{-1}; ^1H NMR δ 1.04 (d, J = 7 Hz, 3 H, CH_3), 1.49 - 1.74 (m, 2 H, CH_2), 1.81 (s, 3 H, CH_3), 1.86 - 2.04 (m, 2 H, CH_2), 2.04 - 2.22 + 2.96 (m, 2 × 1 H, CH_2), 3.30 (m, 1 H, C*H*), 4.88 (m, 1 H, *H*COR), 4.99 (m, 1 H, *H*COR), 5.79 (d, J = 6 Hz, 1 H, C*H*), 6.08 (dd, J = 6/1 Hz, 1 H, C*H*); ^{13}C NMR δ 11.54 (–, CH_3), 19.09 (–, CH_3), 20.12 (+, CH_2), 27.59 (+, CH_2), 42.50 (+, CH_2), 49.80 (–, R_3CH), 89.62 (–, HC*O*R), 89.71 (–, HC*O*R), 94.15 (+, CR_3ONO_2), 127.02 (–, *C*H), 129.72 (–, *C*H), 214.59 (+, *C*O); FAB-MS m/z 254 (M, 28), 209 (11), 191 (14), 121 (14), 107 (19), 96 (37), 89 (38), 77 (29), 63 (10); EA *calc.* C (56.5%), H (6.7%), N (5.5%), O (31.4%) *found* C (56.1%), H (6.7%), N (5.4%); UV/VIS λ_{max} = 207 nm. *Data for* **7**: ^1H NMR δ 1.01 (d, J = 7 Hz, 3 H, CH_3), 1.17 - 1.61 (m, 4 H, 2 × CH_2), 1.95 - 2.23 (m, 2 H, CH_2), 3.16 - 3.37 (m, 1 H, C*H*), 4.99 (m, 1 H, *H*COR), 5.06 (s, 1 H, *H*COR), 5.20 + 5.25 (s, 2 × 1 H, CH_2), 5.67 (m, 1 H, C*H*), 5.96 (m, 1 H, C*H*); MS m/z 192 (M^+, 9), 174 (3), 150 (5), 135 (5), 121 (100), 108 (40), 91 (18), 77 (14), 68 (12), 55 (17).

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23. Due to conformational flexibility of medium sized rings, NOE experiments do not seem to be very promising for elucidating the stereochemical scenario.

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