Pergamon

Tetrahedron Letters 39 (1998) 8259–8262

TETRAHEDRON LETTERS

Synthesis of Dioxatricyclic Segments of Dictyoxetane. Oxygenated 6,8-Dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonanes show Antitumor Activity.

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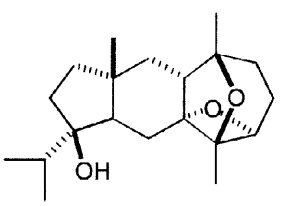
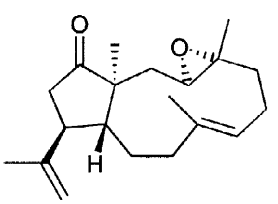
Received 23 July 1998; accepted 6 September 1998

Abstract: Starting from 1,1-bisbenzyloxy propanone four oxetanes **A**, **B**, **C** and **D** representing the dioxatricyclic core of dictyoxetane were synthesized. All of them show a cytotoxic/cytostatic effect using a human gastric carcinoma and a human heptocellular cell line. The activity is comparable to that of 5-fluorouracil.

Dictyoxetane **1** has been isolated from the known brown algae *Dictyota dichotoma*[1] and is structurally related to the class of dolabellanes,[2] which show a wide spectrum of biological activities. For example, the oxygenated diterpene 3,4-epoxy-14-oxo-7,18-dolabelladiene **2**, which contains the characteristic *trans*-bicyclo[9.3.0]tetradecane core, has recently been reported to have antiviral, antibacterial and cytotoxic properties.[3] As yet, the intricate dioxatricyclic framework of **1** has not been encountered in any other natural product.



1
Dictyoxetane
absolute structure unknown



2
3,4-Epoxy-14-oxo-7,18-dolabelladiene

Scheme 1

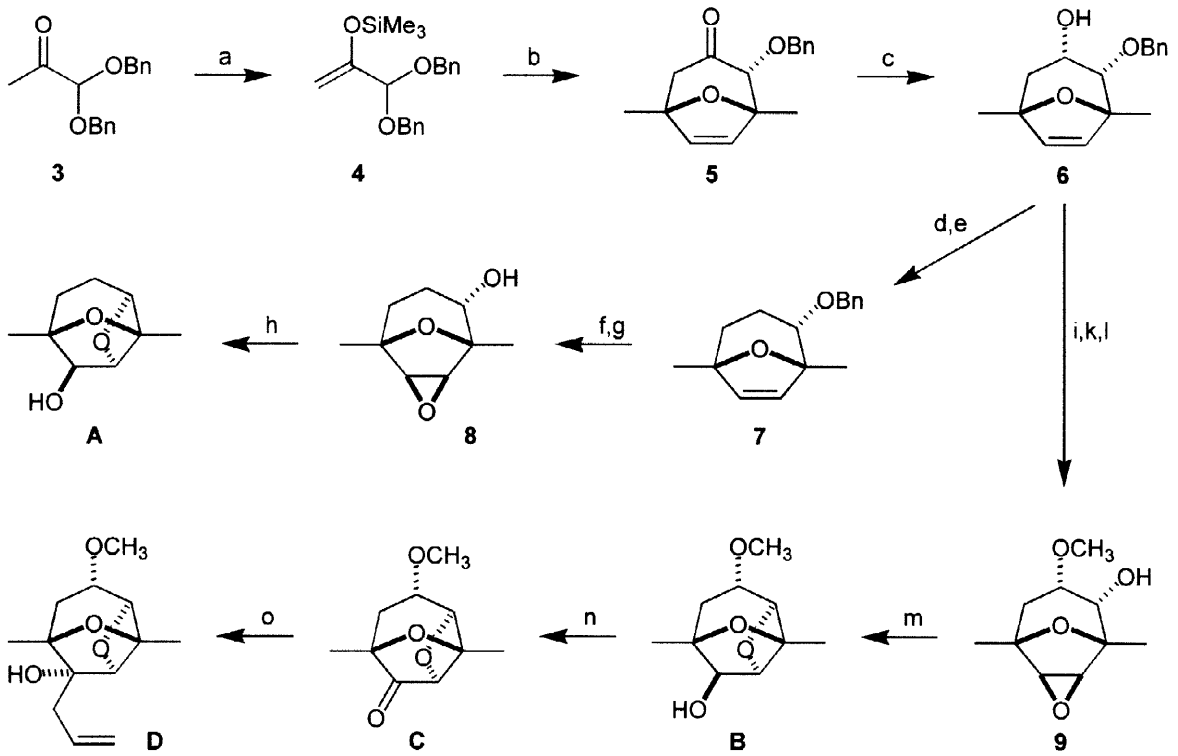
Following some biogenetic speculation we have recently reported a first synthesis of the dioxatricyclic subunit of dictyoxetane.[4,5] We now present an abbreviated and efficient route to oxygenated 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.$0^{3,8}$]nonanes and the first antitumor assays.

Our synthetic approach is outlined in Scheme 2. α-Keto acetal **3** was converted into silyl enol ether **4** and submitted to trimethylsilyl triflate-catalyzed [4+3]-cycloaddition to 2,5-dimethylfuran.[4,6,7] Diastereoselective reduction of **5** provided *endo*-alcohol **6** as advanced precursor of the (i) monooxy series **A** and (ii) bisoxygenated series **B**, **C** and **D**.

0040-4039/98/$ - see front matter
PII: S0040-4039(98)01886-3

Barton-McCombie deoxygenation of hydroxy ether **6** afforded simplified oxabicycle **7**, which was was epoxidized and deprotected. Stereoselective cyclization with $BF_3{\cdot}Et_2O$ in CH_2Cl_2,[8] furnished tricyclic hydroxy oxetane **A** (18% overall with respect to **3**)

Alternatively, the hydroxy group of **6** was methylated. Epoxidation and debenzylation gave epoxy alcohol **9**. In this case, attempted $BF_3{\cdot}Et_2O$-mediated cyclization caused cleavage of the methyl ether to the *endo*-alcohol, which entered into facile 5-*exo*-tet cyclizations with generation of a second tetrahydrofuran unit (two structural isomers). However, base treatment (KOBu^t in THF)[9] afforded the desired tricyclic skeleton **B** in good yield (33% overall with respect to **3**). Swern oxidation provided keto oxetane **C**.[10] The stability of the oxetane segment to Grignard reagents was demonstrated by stereoselective conversion of ketone **C** into *endo*-configurated tertiary homo allylic alcohol **D**.[11]



Scheme 2. a) LDA, TMSCl, THF, -78°C → rt. b) 2,5-dimethylfuran, TMSOTf (catal.), DCM, –78°C, 53% (over 2 steps). c) DIBAH, THF, –78°C, 94%. d) NaH, CS_2, CH_3I, THF, 0°C → rt, 77%. e) Bu_3SnH, AIBN, toluene, 95 °C, 92%. f) *m*-CPBA, DCM, 0°C → rt, 85%. g) H_2, Pd/C, MeOH, 85%. h) $BF_3{\cdot}Et_2O$ (2.1 eq), DCM, 0°C, 72%. i) NaH, CH_3I, THF, 0°C → rt, 100%. k) *m*-CPBA, DCM, 0°C, 97%. l) H_2, Pd/C, MeOH, AcOH, 80%. m) KOBu^t (1.2 eq), THF, rt, 85%. n) DMSO, $(COCl)_2$, DCM, Et_3N, –78°C → rt. o) allylmagnesium bromide, Et_2O, –30 → –10°C, 70%.

The conversion of **9** into oxetane **B** is a cycloisomerization, in which a four-membered ring is formed at the expense of a three-membered ring. This reaction must be preceded by a conformational change in **9**. The six-membered oxacyclic ring has to populate a minor boat, which brings the hydroxy group sufficiently close for a stereoelectronically favoured formation of the new oxetane C-O bond.

The cytostatic and cytotoxic activity of the four dictyoxetane segments **A**, **B**, **C** and **D** was investigated *in vitro*, via the HMO2 (human gastric carcinoma) and the HEP G2 (human heptocellular carcinoma)[12] cell lines.[13] From the concentration-extinction curves the following data were obtained:

Table 1. Antitumor activity (μmol/l) measured toward HMO2 and HEP G2 cells

compound	GI_{50}[a]		TGI[b]		LC_{50}[c]	
	HMO2	HEP G2	HMO2	HEP G2	HMO2	HEP G2
A	4.0	0.1	50	30	> 100	>50
B	3.0	< 0.1	57	45	> 100	>50
C	< 1.0	< 0.1	72	35	> 100	>50
D	< 1.0	< 0.1	54	30	> 100	>50
5-fluorouracil	1.2	0.15	35	50	> 50	>50
cis-platinum	0.1	0.5	2.5	30	40	>50

[a] Drug concentration causing 50% growth inhibition. [b] Drug concentration causing 100% growth inhibition. [c] Drug concentration causing 50% reduction of the cells present at time point zero, i. e at 24 h

It will be seen that all four substrates **A**, **B**, **C** and **D** show cytostatic activity, in the range of 5-fluorouracil, a well known antimetabolite, capable of entering the synthesis and function of nucleic acids, similar to AZT, an anti-AIDS drug.

The most potent substance **C** towards the HMO2 cell line inhibited cell growth by 68% at 1 μmol/l. Although the activity of **C** is lower than that of the structurally far more complex taxol®, both compounds contain a functionalized oxetane ring[16] which is comparatively stable to acid and base.

All title dioxatricyclics represent an entirely new lead structure.

Acknowledgement. We thank the Deutsche Forschungsgemeinschaft (Graduiertenkolleg Chemische und technische Grundlagen der Naturstoffchemie) and the Volkswagenstiftung (Nieders. Vorab) for financial support.

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7 Compound **5**. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): 7.41-7.29 (m, 5 H), 6.06 (d, J = 6 Hz, 1 H), 6.00 (d, J = 6 Hz, 1 H), 5.03 (d, J = 12 Hz, 1 H), 4.58 (d, J = 12 Hz, 1 H), 3.81 (s, 1 H), 2.63 (d, J = 15 Hz, 1 H), 2.44 (dd, J = 15, ≤ 0.5 Hz, 1 H), 1.48 (s, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$, TMS): 206.22, 137.62, 137.12, 134.79, 128.33, 127.89, 87.43, 86.74, 84.79, 74.35, 51.71, 23.05, 20.50. IR (KBr): 1718, 1109, 758 705. MS (rt): no M^+, 167 (35), 91 (100). FAB-MS: 259 (100, M^++1), 258 (15, M^+). HR-MS calcd. for $C_9H_{11}O_3$: 167.0708, found 167.0705.

8 Nonseparable mixture of 96% of the desired oxetane **A** and 4% of starting material **8**. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 4.58-4.55 (m, 1H), 4.54 (s, 1 H), 3.86 (br. s, 1 H), 1.95-1.65 (m, 5 H), 1.55 (s, 3 H), 1.40 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$,TMS): 93.90 (CH), 86.45 (CH), 83.90 (C), 80.90 (C), 81.02 (CH), 27.96 (CH_2), 23.41 (CH_2), 21.84 (CH_3), 19.23 (CH_3). IR ($CHCl_3$): 3616, 3580, 3008, 2936, 996, 972. MS (50°C): 170 (2, M^+), 111 (100). HR-MS calcd. for $C_9H_{14}O_3$: 170.0943, found 170.0942.

9 Compound **B**. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 4.69 (d, J = 1.7 Hz, 1 H), 4.56 (s, 1 H), 3.91 (br. d, J = 6.8 Hz, 1 H), 3.48 (dt, J = 8.6, 1.7 Hz, 1 H), 3.31 (s, 3 H), 2.30 (ddd, J = 13.5, 8.6,≤ 0.5 Hz, 1 H), 1.83 (dd, J = 13.5, 8.6 Hz, 1 H), 1.78 (br. d, J = 6.8 Hz, 1 H), 1.60 (s, 3 H), 1.43 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 94.06 (CH), 84.95 (CH), 83.54 (C), 81.20 (C), 80.61 (CH), 75.28 (CH), 56.09 (CH_3), 34.83 (CH_2), 21.73 (CH_3), 19.24 (CH_3). IR ($CHCl_3$): 3616, 3580, 2936, 1096, 996. MS (rt): 200 (3, M^+), 112 (100). HR-MS calcd. for $C_{10}H_{16}O_4$: 200.1049, found 200.1046.

10 Compound **C** (very hygroscopic). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 5.02 (d, J = 2 Hz, 1 H), 4.37 (s, 1 H), 3.68 (dt, J = 8.5, 2 Hz, 1 H), 3.35 (s, 3 H), 2.34 (dd, J = 14, 8.5 Hz, 1 H), 1.90 (dd, J = 14, 8.5 Hz, 1 H), 1.63 (s, 3 H), 1.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 207.92 (C), 86.65 (CH), 83.93 (CH), 80.10 (C), 78.37 (C), 74.08 (CH), 56.16 (CH_3), 33.94 (CH_2), 20.85 (CH_3), 18.82 (CH_3). IR ($CHCl_3$): 3384, 2936, 1768, 1140, 1100, 1088. MS (rt): no M^+, 169 (4), 141 (100). HR-MS calcd. for $C_{10}H_{14}O_4$: 198.0892, found 198.0883.

11 Compound **D**. ^{1}H NMR (400 MHz, $CDCl_3$, TMS): 5.92-5.81 (dddd, J = 17, 10, 8.5, 6 Hz, 1 H), 5.12 (br. d, J = 10 Hz, 1 H), 5.05 (dq, J = 17, 1.5 Hz, 1 H), 4.83 (d, J = 2 Hz, 1 H), 4.39 (s, 1 H, H-7), 3.48 (dt, J = 8.5, 2 Hz, 1 H), 3.35 (s, 3 H), 3.19 (br. s, 1 H), 2.52 (ddt, J = 14.5, 6, 1.5 Hz, 1 H), 2.25 (dd, J = 14.5, 8.5 Hz, 1 H), 2.10 (m, 2 H), 1.51 (s, 3 H), 1.33 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, TMS): 133.75 (CH), 118.26 (CH_2), 90.43 (CH), 85.97 (CH), 83.30 (C), 78.89 (C), 78.40 (C), 74.80 (CH), 56.09 (CH_3), 37.02 (CH_2), 32.20 (CH_2), 22.31 (CH_3), 19.07 (CH_3). IR ($CHCl_3$): 3532, 3008, 1092. MS (rt): no M^+, 199 (100). MS-FAB: 263 (42, M^++Na), 241 (17, M^++1), 109 (100). HR-MS calcd. for $C_{10}H_{15}O_4$: 240.1362, found 240.1353.

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13 The antitumor activity of the test compounds was determined according to the NCI guidelines.[14] Cells were grown in 96-well microtitre plates (Greiner, Nürtingen, Germany) of RPMI tissue culture medium supplemented with 10% fetal calf serum (Life Technologies, Eggenstein) at 37°C in a humidified atmosphere of 5% CO_2 in air. After 24 h of incubation the test compounds (0.5 - 50 µmol/l (HEP G2), 1 - 100 µmol/l (HMO2)) were added to the cells. Stock solutions of the test compounds were prepared in methanol. After a 48 h incubation in the presence of the test drugs the cells were fixed by addition of trichloroacetic acid and cell protein was assayed with sulforhodamin B.[15]

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