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Synthesis and studies of marine natural products: the dictyoxetane core from 8-oxabicyclo[3.2.1]oct-6-en-3-ones

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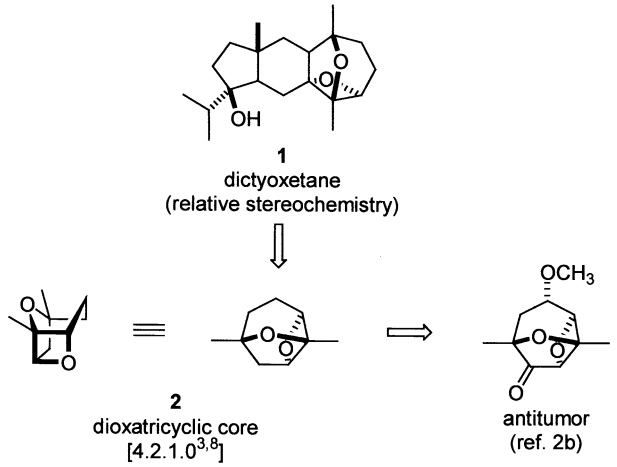
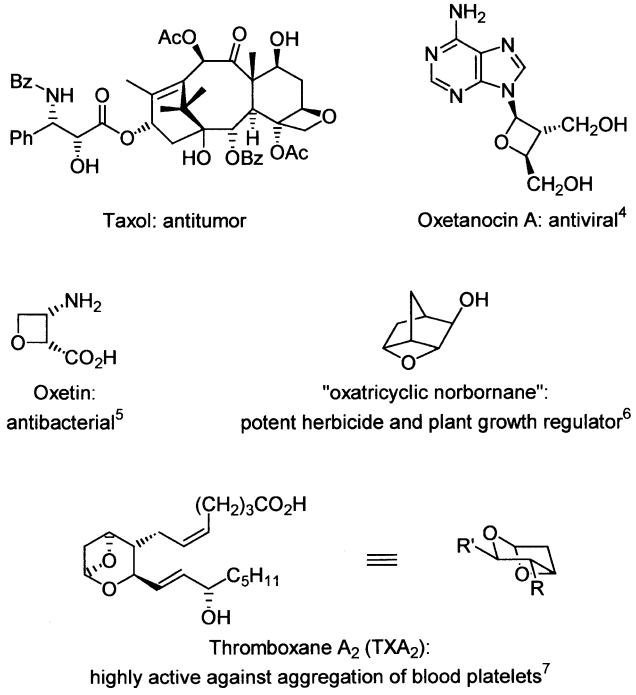
Abstract—Starting from functionalized 8-oxabicyclo[3.2.1]oct-6-en-3-one *rac*-**3** a series of tricyclic epoxy alcohols (**4**, and aminated derivative **16**) have been prepared. After some tuning of the oxygen and nitrogen protecting group at carbon C3 with respect to steric bulk, stability and lipophilicity the highly functionalized tricyclic oxetanes **5** and **17** are accessible in short synthetic order. The structure of key dioxatricycles **9b** and **17** has been corroborated by X-ray crystal diffraction analysis. Biological activities have been evaluated.

Dictyoxetane **1** is related to the class of diterpenoid dolabellanes and has been isolated from the brown algae *Dictyota dichotoma*.[1] Its biogenesis is thought to involve activated geranylgeraniol which cyclizes to a *trans*-configured bicyclo[9.3.0] tetradecane framework.[2a,b] Dictyoxetane **1** is a compact molecule and contains a small ring ether (n=4), three normal ring ethers (n=5–7) and even a medium ring diether (n=8), namely a 1,4-dioxacyclooctane (Scheme 1).

As yet this intricate dioxatricyclic moiety has not been encountered in any other natural product and aside from our earlier work[2] and that of Heathcock,[3] has not been studied further. General interest into naturally occurring oxetanes continues to be high (Scheme 2), because of their variable bioactivity with a spectrum of indications.[4–7] For example, over the last six years at least more than 70 different studies on thromboxane TXA_2 therapy have been reported, mainly in journals of medicine.[8]



Scheme 1.



Scheme 2.

Keywords: tricyclic oxetanes; 6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane; anti-tumor.

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In continuation of our previous work[2] we report progress on the synthesis of the dioxatricyclic substructure and its functionalization. All compounds are potential lead structures and for high-quality libraries.

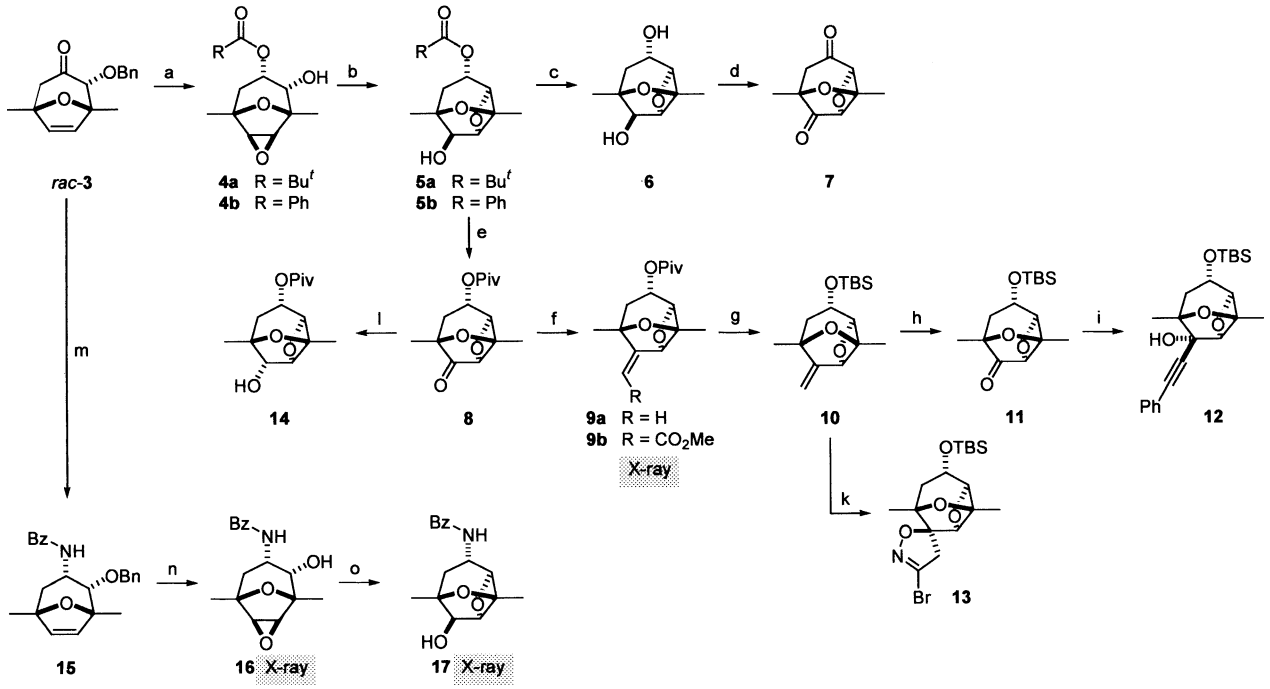
Starting from [4+3] cycloadduct *rac*-**3** we reduced the ketone, protected the resulting hydroxy group and epoxidized the homoallylic double bond. The key four-membered ring closure of epoxy alcohol **4→5** was usually carried out with equimolar $BF_3{\cdot}OEt_2$ and was feasible after benzoyl and pivaloyl protection of the C3(OH) group. The *tert*-butyl ester as protecting group proved to be the best choice for preparing the tricyclic oxetane. Attempts to convert **4** into **5** after *O*-silyl and acetyl protection of C3(OH) were not successful. After cyclization the ester was cleaved reductively to tricyclic diol **6**.[9] A consecutive one-step, double oxidation of diol **6** to diketone **7**, allowed further transformations on the resulting dioxatricyclic framework. Mono-oxidation of hydroxy ester **5** afforded keto ester **8**, which was reduced to epimeric alcohol **14**. Wittig-Olefination of keto ester **8** gave exocyclic olefins **9a** and **9b**. In olefin **9b** the ester group adopts selectively the less hindered *E*-configuration. Reductive deprotection, reprotection (**9a→10**) and oxidative cleavage afforded protected keto alcohol. The silyl protected keto alcohol **11** was converted into alkynyl substituted alcohol **12** with complete stereoselectivity. The exocyclic olefin double bond in **10** also functions as a dipolarophile in a nitrile oxide cycloaddition[10] (**10→13**), again with complete π-facial selectivity. In fact, all nucleophilic additions to the carbonyl group and the pericyclic reaction proceeded selectively from the *exo* face, *trans* to the oxetane oxygen.

Aminated oxetanes were prepared via reductive amination[11] of oxabicyclic ketone **3** and protection as *N*-benzamide giving aminated bicyclic olefin **15**. Epoxidation and debenzylation furnished the *N*-benzoyl protected tricyclic precursor **16** in good yield. Simultaneously, the aminated dictyoxetane framework **17** was formed spontaneously (Scheme 3).

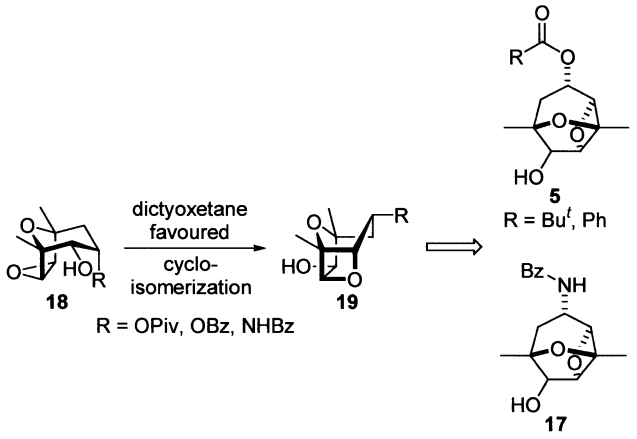
Comparing the conversion of **4→5** with that of **16→17** it was noticeable that the aminated oxetane **17** was formed under mild conditions, proceeding in the presence of weak acid. Formation of oxetane **17** under basic conditions was also feasible, although in low yield. Conformational aspects of the key tricyclizations are shown in Scheme 4. After formation of the tricyclic oxetane **19** the bulky substituent R adopts a less encumbered equatorial position in an oxacyclohexane boat. The structure of two half cage compounds **9b** and **17** occurring late in the synthesis was corroborated by single crystal X-ray diffraction.[12]

1. Conclusion

A remarkably short route to functionalized oxetanes and dictyoxetanes with five and more stereocentres has been described. Our approach is highly flexible providing complex polyoxyfunctionalized tricyclic terpenoids in stereocontrolled fashion. Pivaloyl protection of the free hydroxy group is advantageous to force formation of oxetane from epoxy alcohols **4a** and **4b**. The C3(OH) group (oxabicyclic numbering) appears to be essential to maintain the anti-tumor activity.[13] The dioxatricyclic ester



Scheme 3. *Reagents and conditions*: (a) (i) DIBAH, THF, −78→0°C, 98%; (ii) RCOCl, Py, DMAP, THF, 0°C→rt, 98%; (iii) *m*-CPBA, DCM, 0°C→rt, 1 d, 71%; (iv) Pd/C, H_2 (1 atm), EtOAc, AcOH, 2–3 d, rt, 90%; (b) $BF_3{\cdot}OEt_2$, DCM, 0°C, 69%; (c) DIBAH, THF, −78°C, Na,K-tartrate, 98%; (d) $(COCl)_2$, DMSO, Et_3N, DCM, −78°C→rt, 50%; (e) $(COCl)_2$, DMSO, Et_3N, DCM, −78°C→rt, 77%; (f) $Ph_3P{=}CHR$, DCM, rt, 1 d, 74%; (g) (i) DIBAH, THF, −78°C, 77%; (ii) TBSCl, DCM, Imidazole, rt, 98%; (h) (i) O_3, DCM, 5 min, −78°C; (ii) PPh_3, 1 h, 81%; (i) Phenylacetylene, Bu^tMgCl, THF, −20°C→rt, 81%; (k) $Br_2C{=}N{-}OH$, DBU, acetonitrile, 0°C→rt, 20%; (l) $NaBH_3CN$, MeOH, rt, 1 d, 50%; (m) (i) NH_4OAc, $NaBH_3CN$, MeOH, rt, 2–3 d; (ii) BzCl, Py, DMAP, 0°C, 2 h, 65–80%; (n) (i) *m*-CPBA, DCM, 0°C→rt, 1 d, 82%; (ii) Pd/C, H_2 (1 atm), MeOH, AcOH, 4 d, rt, 49%; (o) LiH, $KOBu^t$, THF, 0°C→rt, 18%.

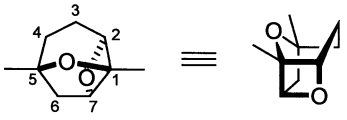


Scheme 4.

rac-**9b** showed cytostatic (10 μMol), but no cytotoxic activity towards tumor cells (cell lines: HepG 7, MCF 7).

2. Experimental

For the sake of clarity the oxabicyclic atom numbering is maintained for the spectral data (^{1}H and ^{13}C) of the oxatricyclics prepared.



2.1. Data for compounds

2.1.1. 2α-Benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one 3. To a solution of [1-(benzyloxy-methoxy-methyl)-vinyloxy]-trimethyl-silane[2c] (3.3 g, 8.6 mmol) in DCM (15 ml) were added 2,5-dimethylfuran (1.40 ml, 13.2 mmol) and TMSOTf (0.30 ml, 1.7 mmol) at −78°C. The mixture was stirred for 3 h and then treated with sat. aq. $NaHCO_3$ solution at rt. The aqueous layer was extracted with DCM and the combined organic phase washed with brine and dried ($MgSO_4$). After removal of the solvent the crude product was purified by column chromatography to afford **3** (1.48 g, 53%), colorless solid, mp 79−80°C. IR (KBr) ν 3034, 2976, 2929, 2874, 1718, 1498, 1454, 1401, 1378, 1340, 1319, 1269, 1243, 1220, 1177, 1109, 758, 705 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.41–7.29 (m, 5H, Ar-H), 6.06 (d, ^3J=6 Hz, 1H, H-7), 6.00 (d, ^3J=6 Hz, 1H, H-6), 5.03 (d, ^2J=12 Hz, 1H, OCH_2Ph), 4.58 (d, ^2J=12 Hz, 1H, OCH_2Ph), 3.81 (s, 1H, H-2), 2.63 (d, ^2J=15 Hz, 1H, H-4ax), 2.44 (dd, ^2J=15 Hz, $J\leq$0.5 Hz, 1H, H-4eq), 1.48 (s, 6H, 2×CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.22 (C, C-3), 137.62 (C, Ar-C), 137.12/134.79 (CH, C-6, C-7), 128.33 (CH, Ar-C), 127.89 (CH, Ar-C), 87.43 (CH, C-2), 86.74/84.79 (C, C-1, C-5), 74.35 (CH_2, OCH_2Ph), 51.71 (CH_2, C-4), 23.05/20.50 (CH_3, 2×CH_3); MS (*m*/*z*) 167 (35, M^+−Bn), 152 (30), 139 (14), 109 (19), 97 (20), 95 (15), 92 (12), 91 (100).

2.1.2. 7α-Pivaloyloxy-1,5-dimethyl-3,9-dioxatricyclo-[3.3.1.0^{2,4}]nonan-6α-ol 4a. To a solution of *rac*-**3** (1.80 g, 6.97 mmol) in THF (7 ml) was added DIBAH (7.0 ml, 8.4 mmol, 1.2 M solution in toluene) at −78°C and the mixture was stirred for 9 h. Then a further portion of DIBAH (3.5 ml) was added and solution was allowed to reach rt over night. The mixture was diluted with MTBE and treated with 2N HCl. The aqueous layer was extracted with DCM (4×) and the combined organic phase dried and concentrated to afford the alcohol (1.78 g, 94%), white solid. IR (KBr) ν 3532, 3073, 2983, 2916, 2850, 1454, 1389, 1354, 1186, 1114, 1051 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40–7.24 (m, 5H, Ar-H), 6.06 (d, ^3J=6 Hz, 1H, H-7), 6.00 (d, ^3J=6 Hz, 1H, H-6), 4.68 (d, ^2J=12 Hz, 1H, OCH_2Ph), 4.49 (d, ^2J=12 Hz, 1H, OCH_2Ph), 4.25–4.16 (m, 1H, H-3), 3.45 (d, ^3J=5.5 Hz, 1H, H-2), 2.58 (d, ^3J=5.5 Hz, 1H, H-2), 2.58 (d, ^3J=3.5 Hz, 1H, OH), 1.93–1.91 (m, 2H, H-4), 1.39 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.45/134.72 (CH, C-6, C-7), 137.46 (C, Ar-C), 128.45 (CH, Ar-C), 128.02 (CH, Ar-C), 84.99/84.14 (C, C-1, C-5), 79.26 (CH, C-2), 71.79 (CH_2, OCH_2Ph), 64.60 (CH, C-3), 39.93 (CH_2, C-4), 23.88/21.24 (CH_3, 2×CH_3); MS (*m*/*z*) 260 (2, M^+), 203 (2), 169 (4, M^+−Bn), 167 (6), 154 (26), 109 (9), 91 (100).

To a solution of the alcohol (2.0 g, 7.6 mmol) in pyridine (6.3 ml) were added DMAP (20 mg) and pivaloyl chloride (1.90 ml, 15.2 mmol) at 0°C. The mixture was stirred for 1 h at 0°C and 8 h at rt, then water and MTBE were added. The aqueous layer was extracted with MTBE (3×) and the combined organic phase washed with 2N HCl and sat. aq. $NaHCO_3$ solution and dried ($MgSO_4$). After removal of the solvent the crude product was purified by chromatography (MTBE/CH) to afford the derived pivaloate (2.45 g, 90%), clear liquid. IR (neat) ν 2973, 2932, 2911, 2871, 1721, 1479, 1455, 1286, 1158, 1095, 1003, 945, 865 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H, Ar-H), 6.07 (d, ^3J=6 Hz, 1H, H-7), 5.96 (d, ^3J=6 Hz, 1H, H-6), 5.49 (dt, ^3J=5.4, 1.25 Hz, 1H, H-3), 4.56 (d, ^2J=11 Hz, 1H, OCH_2Ph), 4.32 (d, ^2J=11 Hz, 1H, OCH_2Ph), 3.52 (d, ^3J=5.4 Hz, 1H, H-2), 2.06 (dd, ^2J=15 Hz, ^3J=5.4 Hz, 1H, H-4ax), 1.71 (dd, ^2J=15 Hz, ^3J=1.25 Hz, 1H, H-4eq), 1.44 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.17 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.95 (C, C8), 137.95 (C, Ar-C), 137.22/135.26 (CH, C-6, C-7), 128.53/128.26 (CH, *o*-, *m*-Ar-C), 127.93 (CH, *p*-Ar-C), 85.65/83.85 (C, C-1, C-5), 78.87 (CH, C-2), 72.05 (CH_2, OCH_2Ph), 65.55 (CH, C-3), 40.19 (C, *C*(CH_3)), 39.07 (CH_2, C-4), 27.11 (CH_3, C(*C*H_3)$_3$), 23.66 (CH_3, CH_3), 21.07 (CH_3, CH_3); MS (*m*/*z*) 344 (2, M^+), 253 (2, M^+−C_7H_7), 242 (2), 181 (6), 151 (24), 136 (54), 109 (11), 93 (28), 91 (100).

To a solution of the pivaloate (640 mg, 1.86 mmol) in DCM (5.8 ml) was added *m*-CPBA (520 mg, 3.70 mmol) portion-wise at 0°C. The mixture was stirred for 4 h at 0°C, then water and DCM were added. The aqueous layer was extracted several times with DCM and the combined organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by chromatography (MTBE/CH) to afford the epoxide (600 mg, 89%), white solid. IR (neat) ν 2974, 2933, 2872, 1724, 1454, 1283, 1151, 1106, 900, 954, 918, 739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H, Ar-H), 5.52 (dt, ^3J=4.8, 1.6 Hz, 1H, H-3), 4.59 (d, ^2J=11 Hz, 1H, OCH_2Ph), 4.34 (d, ^2J=11 Hz, 1H, OCH_2Ph), 3.67 (d, ^3J=3 Hz, 1H, H-7), 3.47 (d, ^3J=4.8 Hz, 1H, H-2), 3.41 (d, ^3J=3 Hz, 1H, H-6),

2.05 (dd, ^2J=15.4 Hz, ^3J=4.8 Hz, 1H, H-4ax), 1.82 (dd, ^2J=15.4 Hz, ^3J=1.5 Hz, 1H, H-4eq), 1.39 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.17 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.48 (C, C8), 137.43 (C, Ar-C), 128.33/128.23 (CH, *o*-, *m*-Ar-C), 127.93 (CH, *p*-Ar-C), 79.21/76.93 (C, C-1, C-5), 78.19 (CH, C-2), 72.15 (CH_2, O*C*H_2Ph), 64.98 (CH, C-3), 58.02/56.89 (CH, C-6, C-7), 39.13 (CH_2, C-4), 38.75 (C, *C*(CH_3)), 27.17 (CH_3, C(*C*H_3)$_3$), 19.79 (CH_3, CH_3), 17.28 (CH_3, CH_3); MS (*m*/*z*) 360 (5, M^+), 274 (7), 258 (6), 215 (3), 190 (6), 167 (26), 152 (24), 125 (9), 109 (7), 91 (100).

A mixture of the epoxide (2.58 g, 7.17 mmol), AcOH (1 ml) and a catalytic amount of Pd/C in EtOH (49 ml) was hydrogenated for 2 d at rt. After complete reaction the mixture was filtered through a short column and the column washed with MTBE/EA. The filtrate was evaporated, the residue dissolved in MTBE and extracted with sat. aq. $NaHCO_3$ solution (3×) and brine. The aqueous layer was extracted with MTBE, the combined organic phase dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography (MTBE/CH) to give **4a** (1.75 g, 90%), white solid. IR ($CHCl_3$) ν 3591, 2979, 2935, 2875, 1714, 1479, 1285, 1230, 1150, 1119, 952, 874 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (ddd, ^3J=5, 1.4 Hz, 1H, H-3), 3.75 (d, ^3J=5 Hz, 1H, H-2), 3.60 (d, ^3J=3 Hz, 1H, H-7), 3.30 (d, ^3J=3 Hz, 1H, H-6), 2.26 (br s, 1H, OH), 2.06 (dd, ^2J=15.4 Hz, ^3J=5 Hz, 1H, H-4ax) 1.83 (dd, ^2J=15.4 Hz, ^3J=1.4 Hz, 1H, H-4eq), 1.41 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 1.21 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.04 (C, C-8), 79.19/76.69 (C, C-1, C-5), 72.48 (CH, C-2), 69.08 (CH, C-3), 57.82/56.44 (CH, C-6, C-7), 38.91 (C, *C*(CH_3)$_3$), 38.74 (CH_2, C-4), 27.19 (C, C(*C*H_3)$_3$), 19.75/16.94 (CH_3, 2×CH_3); MS (*m*/*z*) 270 (2, M^+), 213 (18), 185 (5), 168 (67), 129 (40), 112 (16), 95 (100), 85 (96), 82 (74).

2.1.3. 7α-Benzoyloxy-1,5-dimethyl-3,9-dioxatricyclo-[3.3.1.0^{2,4}]nonan-6α-ol 4b. Epoxide (1.71 g, 4.5 mmol) in EA (32 ml) and AcOH (0.7 ml) was hydrogenated for 2 d as described for **4a** to give after chromatography (MTBE/CH) **4b** (1.17 g, 90%), white solid. IR (neat) ν 3502, 2981, 2961, 2872, 1715, 1602, 1452, 1364, 1275, 1224, 1112, 1026, 957, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (m, 2H, *o*-Ar-H), 7.57 (m, 1H, *p*-Ar-H), 7.43 (m, 2H, *m*-Ar-H), 5.25 (dt, ^3J=4.8, 1.3 Hz, 1H, H-3), 3.84 (d, ^3J=4.9 Hz, 1H, H-2), 3.77 (d, ^3J=3 Hz, 1H, H-7); 3.56 (d, ^3J=3 Hz, 1H, H-6), 2.62 (br s, 1H, OH), 2.17 (dd, ^2J=15.6 Hz, ^3J=4.8 Hz, 1H, H-4ax), 2.02 (dd, ^2J=15.6 Hz, ^3J=1.3 Hz, 1H, H-4eq), 1.45 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.81 (C, C=O), 133.54 (CH, *p*-Ar-C), 129.58 (C, Ar-C), 129.51/128.65 (CH, *o*-, *m*-Ar-C), 79.35/76.79 (C, C-1, C-5), 72.35 (CH, C-2), 69.88 (CH, C-3), 57.91/56.53 (CH, C-6, C-7), 38.81 (CH_2, C-4), 19.76/16.96 (CH_3, 2×CH_3); MS (60°C) (*m*/*z*) 233 (5), 168 (17), 150 (2), 139 (3), 125 (5), 105 (100), 95 (18), 82 (19).

2.1.4. 4α-Pivaloyloxy-6,8-dimethyl-2,7-dioxatricyclo-[4.2.1.0^{3,8}]nonan-9β-ol 5a. To a solution of epoxide **4a** (1.75 g, 6.48 mmol) in DCM (44 ml) was added $BF_3{\cdot}Et_2O$ (1.63 ml, 13.0 mmol) at 0°C. The mixture was stirred for 5 h at 0°C and 5 h at rt. Then sat. aq. $NaHCO_3$ was added to the dark red solution and the aqueous layer was extracted several times with DCM. The combined organic phase was washed with brine, dried (Na_2SO_4), evaporated and purified by column chromatography (MTBE/CH) to afford **5a** (1,25 g, 71%), white solid. IR ($CHCl_3$) ν 3618, 2976, 2935, 2875, 1723, 1479, 1282, 1230, 1156, 1046, 995, 936 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (dt, ^3J=8, 1.8 Hz, 1H, H-3), 4.61 (d, ^3J=1.75 Hz, 1H, H-2), 4.59 (s, 1H, H-7), 3.95 (s, 1H, H-6), 2.34 (ddd, ^2J=13.3 Hz, ^3J=8.66, 0.75 Hz, 1H, H-4eq), 1.87 (dd, ^2J=13.3 Hz, ^3J=9.16 Hz, 1H, H-4ax), 1.61 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.18 (s, 9H, C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.94 (C, C-8), 94.28 (CH, C-2), 86.10 (CH, C-7), 83.69/81.56 (C, C-1, C-5), 80.55 (CH, C-6), 69.18 (CH, C-3), 38.77 (C, *C*(CH_3)$_3$), 34.13 (CH_2, C-4), 27.07 (C, C(*C*H_3)$_3$), 21.60/19.14 (CH_3, 2×CH_3); MS (*m*/*z*) 270 (10, M^+), 209 (7), 186 (17), 168 (19), 139 (28), 125 (29), 112 (100), 95 (50), 85 (46).

2.1.5. 4α-Benzoyloxy-6,8-dimethyl-2,7-dioxatricyclo-[4.2.1.0^{3,8}]nonan-9β-ol 5b. Hydroxy epoxide **4b** (297 mg, 1.03 mmol) and $BF_3{\cdot}OEt_2$ (0.26 ml, 2.0 mmol) in DCM (17 ml) were allowed to react as described for **5a** to afford after chromatography (MTBE) **5b** (205 mg, 69%), white solid. IR (neat) ν 3403, 2981, 2939, 1715, 1450, 1377, 1263, 1199, 1110, 1070, 981, 920, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H, *o*-Ar-H), 7.54 (m, 1H, *p*-Ar-H), 7.43 (m, 2H, *m*-Ar-H), 5.21 (dt, ^3J=8.8, 1.9 Hz, 1H, H-3), 4.78 (d, ^3J=1.6 Hz, 1H, H-2), 4.66 (s, 1H, H-7), 4.02 (s, 1H, H-6), 2.49 (dd, ^2J=13.4 Hz, ^3J=8.8 Hz, 1H, H-4eq), 2.17 (br s, 1H, OH), 2.05 (dd, ^2J=13.5 Hz, ^3J=9.2 Hz, 1H, H-4ax), 1.67 (s, 3H, CH_3), 1.50 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.87 (C, C=O), 133.21 (CH, *p*-Ar-C), 129.78 (C, Ar-C), 129.75/128.36 (CH, *o*-, *m*-Ar-C), 94.35 (CH, C-2), 86.14 (CH, C-7), 83.78/81.61 (C, C-1, C-5), 80.56 (CH, C-6), 70.05 (CH, C-3), 34.32 (CH_2, C-4), 21.61/19.15 (CH_3, 2×CH_3); MS (100°C) (*m*/*z*) 290 (4, M^++1), 229 (5), 185 (5), 168 (6), 150 (4), 125 (6), 112 (38), 105 (100), 95 (8), 77 (16).

2.1.6. 6,8-Dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-4α,9β-diol 6. To a solution of ester **5a** (130 mg, 0.48 mmol) in THF (3 ml) was added DIBAH (1.32 ml, 1.58 mmol, 1.2 M solution in toluene) at −78°C. The mixture was stirred for 1 h at −78°C and then allowed to reach rt slowly. MTBE/EA was added followed by sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution (1 ml). The aqueous layer was extracted with MTBE/EA and the combined organic phase was washed with brine and dried (Na_2SO_4). The solvent was removed and the residue purified by chromatography (MTBE) to afford **6** (88 mg, 98%), highly viscous oil. IR (neat) ν 3420, 2974, 2938, 2912, 2874, 1458, 1281, 1152, 1075, 989, 937 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 4.85 (dt, ^3J=9.04, 1.86 Hz, 1H, H-3), 4.59 (d, ^3J=1.75 Hz, 1H, H-2), 4.56 (s, 1H, H-7), 3.88 (s, 1H, H-6), 2.31 (dd, ^2J=13.4 Hz, ^3J=8.8, 0.75 Hz, 1H, H-4eq), 1.83 (dd, ^2J=13.4 Hz, ^3J=9.16 Hz, 1H, H-4ax), 1.59 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 96.28 (CH, C-2), 87.58 (CH, C-7), 85.19/82.84 (C, C-1, C-5), 81.46 (CH, C-6), 70.93 (CH, C-3), 35.39 (CH_2, C-4), 21.92/19.08 (CH_3, 2×CH_3); MS (*m*/*z*) 186 (100, M^+), 168 (4), 139 (6), 125 (10), 112 (48), 95 (12), 85 (16).

2.1.7. 1,5-Dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-4,9-dione 7. To a solution of oxalyl chloride (0.15 ml, 2.5 mmol) in DCM (7 ml) was added DMSO (0.23 ml, 5.6 mmol) at −78°C, followed by tricyclic alcohol **6** (118 mg, 0.600 mmol) in DCM (3 ml). The mixture was stirred for 1 h at −78°C and then NEt_3 (1.1 ml) was added. Stirring was continued for 1 h at −78°C and 1.5 h at rt. The solvent was removed, the residue dissolved in MTBE and treated with water. The aqueous layer was extracted several times with MTBE. The combined organic phase was dried (Na_2SO_4) and evaporated. Column chromatography (MTBE/CH) afforded **7** (54 mg, 50%), light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65/4.63 (s, 2H, H-2, H-7) 3.04 (d, ^2J=18 Hz, 1H, H-4ax), 2.65 (d, ^2J=18 Hz, 1H, H-4ax), 1.71 (s, 3H, CH_3), 1.49 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.75 (C=O, C-6), 201.46 (C=O, C-3), 89.85/58.83 (CH, C-7, C-2), 81.21/79.95 (C, C-1, C-5), 46.50 (CH_2, C-4), 20.71/18.95 (CH_3, 2×CH_3).

2.1.8. 4α-Pivaloyloxy-6,8-dimethyl-2,7-oxatricyclo-[4.2.1.0^{3,8}]nonan-9-one 8. Tricyclic alcohol **5a** (700 mg, 0.85 mmol), oxalyl chloride (0.32 ml, 3.5 mmol), DMSO (0.51 ml, 7.9 mmol) and NEt_3 (2.5 ml) in DCM (22 ml) were allowed to react as described for **7** to give after chromatography (MTBE/CH) **8** (537 mg, 77%), light yellow oil. IR (neat) ν 2979, 2936, 2874, 1721, 1615, 1458, 1364, 1281, 1149, 1037, 939 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.09 (dt, ^3J=8.4, 2.3 Hz, 1H, H-3), 4.93 (d, ^3J=2.3 Hz, 1H, H-2), 4.39 (s, 1H, H-7), 2.40 (dd, ^2J=14 Hz, ^3J=8.4 Hz, 1H, H-4eq), 1.88 (dd, ^2J=14 Hz, ^3J=8.4 Hz, 1H, H-4ax), 1.64 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.18 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.75 (C=O, C-6), 177.78 (C, C-8), 87.42 (CH, C-7), 84.12 (CH, C-2), 80.16/78.69 (C, C-1, C-5), 67.76 (CH, C-3), 38.79 (C, *C*(CH_3)$_3$), 33.42 (CH_2, C-4), 27.03 (C, C(*C*H_3)$_3$), 20.71/18.75 (CH_3, 2×CH_3); MS (100°C) (*m*/*z*) 269 (2, M^++1), 255 (14), 182 (22), 140 (19), 139 (17), 127 (11), 125 (15), 112 (32), 98 (49), 86 (100), 71 (55).

2.1.9. 9-Methylene-4α-pivaloyloxy-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane 9a. To a solution of methyl triphenylphosphonium bromide (814 mg, 2.28 mmol) in THF (4 ml) was added *n*-BuLi (1.40 ml, 2.24 mmol, 1.6 M solution in hexane) at 0°C. After 30 min the mixture was cooled to −78°C and ketone **8** (510 mg, 1.90 mmol) in THF (3 ml) was added. The mixture was allowed to reach rt within 1 d and then treated with water and MTBE. The aqueous layer was extracted with MTBE, the combined organic phase was washed with brine and dried (Na_2SO_4). After removal of the solvent the residue was purified by chromatography (MTBE/CH) to give **9a** (270 mg, 53%), colorless solid. IR ($CHCl_3$) ν 2957, 2932, 2873, 1719, 1460, 1282, 1146, 1098, 1036, 927, 912, 851 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, ^2J=17.7 Hz, 2H, H-8), 4.98 (ddd, ^3J=9.03, 8.41, 2.14 Hz, 1H, H-3), 4.89 (s, 1H, H-7), 4.71 (d, ^3J=2.13 Hz, 1H, H-2), 2.45 (dd, ^2J=13.2 Hz, ^3J=9.03 Hz, 1H, H-4eq), 1.88 (dd, ^2J=13.2 Hz, ^3J=8.41 Hz, 1H, H-4ax), 1.59 (s, 3H, CH_3), 1.55 (s, 3H, CH_3), 1.19 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.97 (C, C=O), 153.94 (C, C-6), 108.74 (CH_2, C-10), 91.32 (CH, C-2), 85.95 (CH, C-7), 81.05/80.71 (C, C-1, C-5), 68.81 (CH, C-3), 38.76 (C, *C*(CH_3)$_3$), 37.32 (CH_2, C-4), 27.09 (C, C(*C*H_3)$_3$), 24.04/18.72 (CH_3, 2×CH_3); MS (*m*/*z*) 266 (1, M^+), 181 (5), 164 (31), 149 (6), 135 (7), 121 (13), 110 (100), 109 (28), 95 (9), 85 (5).

2.1.10. [4α-Pivaloyloxy-6,8-dimethyl-2,7-dioxatricyclo-[4.2.1.0^{3,8}]nonan-9-ylidene]-acetic acid methyl ester 9b. To a solution of ylide (250 mg, 0.72 mmol) in DCM (2 ml) was added ketone **8** (90 mg, 0.34 mmol) in DCM (2 ml) and the resulting mixture was stirred for 16 h at rt. To complete the reaction a further portion of ylide (170 mg, 0.48 mmol) was added and stirring was continued for 1 d. Water and DCM were added and the aqueous layer was extracted several times with DCM. The combined organic phase was dried (Na_2SO_4) and the solvent removed. The crude product was purified by column chromatography (MTBE/CH) to give **9b** (90 mg, 82%), colorless solid. IR (neat) ν 2968, 2934, 2872, 1718, 1681, 1440, 1357, 1279, 1222, 1144, 1037, 930 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (s, 1H, H-10), 5.83 (s, 1H, H-7), 4.96 (dt, ^3J=8.7, 2.3 Hz, 1H, H-3), 4.72 (d, ^3J=2.3 Hz, 1H, H-2), 3.74 (s, 3H, OCH_3), 2.45 (dd, ^2J=13.4 Hz, ^3J=9 Hz, 1H, H-4eq), 1.82 (dd, ^2J=13.4 Hz, ^3J=8.5 Hz, 1H, H-4ax), 1.58 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 1.15 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.91 (C, C-8), 165.96 (C, C-11), 161.75 (C, C-6), 112.93 (CH, C-10), 86.16 (CH, C-7), 85.82 (CH, C-2), 81.74/80.57 (C, C-1, C-5), 68.44 (CH, C-3), 38.74 (C, *C*(CH_3)$_3$), 37.12 (CH_2, C-4), 27.06 (C, C(*C*H_3)$_3$), 23.79/18.69 (CH_3, 2×CH_3); MS (*m*/*z*) 324 (4, M^+), 293 (4), 222 (54), 190 (5), 180 (6), 169 (11), 168 (100), 135 (7), 109 (13), 85 (5). For X-ray crystal structure see Ref. 12.

2.1.11. 9-Methylene-4α-*tert*-butyldimethylsilyloxy-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonane 10. Ester **9a** (200 mg, 0.75 mmol) and DIBAH (1.65 ml, 1.2 M solution in toluene) were allowed to react as described for compound **6** to afford after chromatography (MTBE) the alcohol (90 mg, 66%), colorless solid. IR ($CHCl_3$) ν 3443, 2993, 2967, 2941, 1413, 1375, 1262, 1186, 1130, 1054, 966, 913, 881, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (d, ^2J=16.8 Hz, 2H, H-8), 4.84 (s, 1H, H-7), 4.59 (d, ^3J=2.51 Hz, 1H, H-2), 3.84 (ddd, ^3J=9.04, 7.78, 2.5 Hz, 1H, H-3), 2.69 (s, 1H, OH), 2.39 (dd, ^2J=13.6 Hz, ^3J=9.04 Hz, 1H, H-4eq), 1.68 (dd, ^2J=13.6 Hz, ^3J=7.78 Hz, 1H, H-4ax), 1.54 (s, 3H, CH_3), 1.47 (s, 3H, CH_3); ^{13}C NMR (100 MHz,$CDCl_3$) δ 154.14 (C, C-6), 108.67 (CH_2, C-10), 91.06 (CH, C-2), 88.34 (CH, C-7), 81.03/80.09 (C, C-1, C-5), 66.19 (CH, C-3), 41.31 (CH_2, C-4), 24.05/18.75 (CH_3, 2×CH_3); MS (*m*/*z*) 182 (1, M^+), 164 (2), 138 (2), 121 (7), 110 (100), 109 (30), 95 (19), 87 (9), 79 (3).

To a solution of the alcohol (60 mg, 0.33 mmol) and imidazole (56 mg, 0.82 mmol) in DMF (1 ml) was added TBDMSCl (64 mg, 0.39 mmo) at rt and the mixture was stirred for 16 h. DCM and water were added and the aqueous layer was extracted with DCM. The combined organic phase was washed with brine and dried (Na_2SO_4) to afford **10** (96 mg, 98%), colorless solid. IR ($CHCl_3$) ν 2951, 2928, 2881, 2855, 1472, 1458, 1382, 1251, 1132, 1083, 934, 832, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 (d, ^2J=17.4 Hz, 2H, H-8), 4.82 (s, 1H, H-7), 4.53 (d,

^3J=2.26 Hz, 1H, H-2), 3.95 (ddd, ^3J=8.78, 8.15, 2.26 Hz, 1H, H-3), 2.23 (dd, ^2J=13.3 Hz, ^3J=8.78 Hz, 1H, H-4eq), 1.88 (dd, ^2J=13.3 Hz, ^3J=8.16 Hz, 1H, H-4ax), 1.56 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.06/0.05 (s, 6H, 2×SiC); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.26 (C, C-6), 108.26 (CH_2, C-10), 90.81 (CH, C-2), 88.76 (CH, C-7), 81.08/80.34 (C, C-1, C-5), 67.37 (CH, C-3), 41.25 (CH_2, C-4), 25.83 (CH_3, $SiC(CH_3)_3$), 24.17/18.86 (CH_3, 2×CH_3), 18.13 (C, $SiC(CH_3)_3$), −4.57/−4.79 (CH_3, 2×$SiCH_3$); MS (*m/z*) 272 (5), 239 (5, $M^+-C_4H_9$), 221 (32), 197 (23), 179 (16), 147 (20), 135 (7), 129 (36), 123 (99), 110 (100), 105 (40), 95 (14), 75 (79).

2.1.12. 4α-*tert*-Butyldimethylsilyloxy-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9-one 11. A solution of olefin **10** (43 mg, 0.14 mmol) in DCM (2 ml) was ozonolyzed at −78°C until the blue color persists. The excess ozone was removed by a stream of nitrogen and the resulting colorless solution was treated with Ph_3P (114 mg, 0.430 mmol) in DCM (1 ml). After removal of the solvent the crude product was purified by chromatography (MTBE/CH) to give **11** (35 mg, 81%), colorless oil. IR ($CHCl_3$) ν 2930, 2885, 2856, 1762, 1471, 1390, 1372, 1252, 1134, 1082, 1063, 936, 834, 777 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (d, ^3J=2.35 Hz, 1H, H-2), 4.35 (s, 1H, H-7), 4.10 (ddd, ^3J=8.8, 8.15, 2.26 Hz, 1H, H-3), 2.18 (dd, ^2J=14.1 Hz, ^3J=8.8 Hz, 1H, H-4eq), 1.90 (dd, ^2J=14.1 Hz, ^3J=8.15 Hz, 1H, H-4ax), 1.63 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 0.89 (s, 9H, $SiC(CH_3)_3$), 0.083/0.081 (s, 6H, 2×$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.12 (C, C-6), 89.40 (CH, C-2), 82.71 (CH, C-7), 79.25/77.39 (C, C-1, C-5), 65.55 (CH, C-3), 36.15 (CH_2, C-4), 24.74 (CH_3, $SiC(CH_3)_3$), 19.85/17.89 (CH_3, 2×CH_3), 17.07 (C, $SiC(CH_3)_3$), −5.61/−5.77 (CH_3, 2×$SiCH_3$); MS (80°C) (*m/z*) 269 (1), 241 (100, $M^+-C_4H_9$), 213 (16), 199 (41), 181 (55), 171 (23), 157 (7), 143 (29), 129 (74), 115 (18), 109 (9), 85 (11), 75 (51).

2.1.13. 4α-*tert*-Butyldimethylsilyloxy-9-phenylethynyl-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9α-ol 12. To a solution of phenyl acetylene (0.02 ml, 0.15 mmol) in THF was added *t*-BuMgCl (0.09 ml, 0.15 mmol, 2 M solution in E) at 0°C. The mixture was stirred for 1 h at 0°C and then cooled to −20°C. A solution of ketone **11** (30 mg, 0.1 mmol) in THF (1 ml) was added dropwise and the mixture was stirred for 2 h at 0°C and then allowed to reach rt overnight. MTBE was added, followed by sat. aq. NH_4Cl solution and sat. aq. Na,K tartrate solution (1 ml). The aqueous layer was extracted with MTBE, the combined organic phase washed with brine and dried (Na_2SO_4). Removal of the solvent and chromatography (MTBE/CH) gave **12** (32 mg, 81%), colorless solid. IR (neat) ν 3393, 2929, 2856, 1598, 1462, 1444, 1390, 1375, 1252, 1137, 1082, 1005, 938, 836, 776 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.28 (m, 5H, Ar-H), 4.65 (d, ^3J=1.88 Hz, 1H, H-2), 4.62 (s, 1H, H-7), 3.94 (dt, ^3J=8.16, 2.13 Hz, 1H, H-3), 2.25 (dd, ^2J=14.4 Hz, ^3J=8.3 Hz, 1H, H-4eq), 2.05 (dd, ^2J=14.4 Hz, ^3J=8 Hz, 1H, H-4ax), 1.61 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 0.90 (s, 9H, $SiC(CH_3)_3$), 0.010/0.096 (s, 6H, 2×$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.83/128.66 (CH, *o*-, *m*-Ar-C), 128.24 (CH, *p*-Ar-C), 122.22 (C, Ar-C), 90.29 (CH, C-2), 88.43 (C, C-9), 88.08 (CH, C-7), 83.58 (C, C-8), 80.91/79.77 (C, C-1, C-5), 79.54 (C, C-6), 66.75 (CH, C-3), 34.50 (CH_2, C-4), 24.21 (CH_3, $SiC(CH_3)_3$), 19.37/19.09 (CH_3, 2×CH_3), 18.16 (C, $SiC(CH_3)_3$), −4.55/−4.78 (CH_3, 2×$SiCH_3$); MS (100°C) (*m/z*) 343 (39, $M^+-C_4H_9$), 325 (14), 293 (15), 285 (5, $M^+-SiMe_2{}^tBu$), 257 (18), 241 (23), 225 (100), 201 (39), 185 (12), 161 (3), 129 (31), 109 (46), 91 (7), 101 (7), 77 (11), 75 (51).

2.1.14. 4α-*tert*-Butyldimethylsilyloxy-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9-spiro-(12-aza-11-bromo)-oxazoline 13. To a solution of dibromohydroxyl amine (65 mg, 0.32 mmol) in MeCN (0.1 ml) was added alkene **10** (38 mg, 0.13 mmol) and the mixture was cooled to 0°C. DBU (57 μl, 0.38 mmol) was added dropwise. The mixture was stirred for 1 h at rt and then quenched by addition of water. The aqueous layer was extracted with EA and the combined organic phase was dried (Na_2SO_4) and evaporated. The resulting crude product was purified by chromatography (MTBE/EA) to afford **13** (27 mg, 50%), colorless oil. IR (neat) ν 2953, 2929, 2883, 2856, 1472, 1389, 1374, 1253, 1133, 1083, 1006, 935, 834, 775 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (d, ^3J=1.90 Hz, 1H, H-2), 4.46 (s, 1H, H-7), 3.94 (ddd, ^3J=8.5, 8.37, 1.92 Hz, 1H, H-3), 3.52 (d, ^2J=18 Hz, 1H, H-8), 3.08 (d, ^2J=18 Hz, 1H, H-8), 2.13 (dd, ^2J=13.7 Hz, ^3J=8.37 Hz, 1H, H-4eq), 1.71 (dd, ^2J=13.86 Hz, ^3J=8.5 Hz, 1H, H-4ax), 1.63 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.06/0.05 (s, 6H, 2×$SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.63 (C, C-9), 96.14 (C, C-6), 90.91 (CH, C-2), 89.49 (CH, C-7), 83.24/80.95 (C, C-1, C-5), 67.18 (CH, C-3), 41.28 (CH_2, C-4), 37.68 (CH_2, C-8), 25.80 (CH_3, $SiC(CH_3)_3$), 20.72/18.83 (CH_3, 2×CH_3), 18.15 (C, $SiC(CH_3)_3$), −4.56/−4.71 (CH_3, 2×$SiCH_3$); MS (60°C) 281 (2), 263 (2), 239 (69), 221 (35), 197 (26), 179 (13), 147 (20), 143 (23), 129 (32), 123 (100), 117 (14), 110 (89), 109 (79), 105 (33), 75 (63).

2.1.15. 4α-Pivaloyloxy-9-hydroxy-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]non-4-yl ester 14. To a solution of ketone **8** (130 mg, 0.48 mmol) in dry MeOH (1.5 ml) was added dry NH_4OAc (375 mg, 10.0 mmol) and the mixture was stirred vigorously. Then $NaBH_3CN$ (22 mg, 0.33 mmol) was added portionwise within 30 min. The resulting mixture was stirred for 2 d at rt and then acidified (concd. HCl, pH 2–3) and the solvent was removed. The residue was dissolved in MTBE (100 ml) and water (10 ml) was added. The aqueous layer was saturated with KOH and extracted with EA/MTBE (3×). The combined organic layer was dried ($MgSO_4$) and evaporated. Reductive amination of the carbonyl group was the minor reaction in this case (cf. **15** below). To a solution of crude amine, DMAP (catal.) and NEt_3 (0.1 ml) in THF (1 ml) was added benzoyl chloride (50 μl, 0.43 mmol) dropwise at 0°C. The mixture was stirred for 1 h at 0°C and 8 h at rt. Water and MTBE were added and the aqueous layer was extracted with MTBE (3×). The combined organic layer was washed with 2N HCl, sat. aq. $NaHCO_3$ solution and dried ($MgSO_4$). After removal of the solvent and chromatography α-alcohol **14** (64 mg, 50%) and the product of reductive amination (36 mg, 20%) were obtained. Data for **14**, colorless solid: IR ($CHCl_3$) ν 3618, 2976, 2935, 2875, 1723, 1479, 1282, 1230, 1156, 1046, 995, 936 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 4.83 (dt, ^3J=9, 1.9 Hz, 1H, H-3), 4.69 (d, ^3J=1.63 Hz, 1H, H-2), 4.58 (d, ^3J=4.3 Hz, 1H, H-7), 3.55 (d, ^3J=4.4 Hz, 1H, H-6), 2.34

(dd, ^2J=13.3 Hz, ^3J=9 Hz, 1H, H-4eq), 1.95 (dd, ^2J=13.3 Hz, ^3J=8.53 Hz, 1H, H-4ax), 1.51 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.20 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, CD_3OD) δ 177.44 (C, C-8), 88.40 (CH, C-2), 86.00 (CH, C-7), 80.00/79.69 (C, C-1, C-5), 76.84 (CH, C-6), 68.79 (CH, C-3), 37.79 (C, $C(CH_3)_3$), 28.26 (CH_2, C-4), 25.48 (C, $C(CH_3)_3$), 23.84/ 17.30 (CH_3, 2×CH_3); MS (*m*/*z*) 270 (10, M^+), 209 (7), 186 (17), 168 (19), 139 (28), 125 (29), 112 (100), 95 (50), 85 (46).

2.1.16. 3α-*N*-Benzoylamino-2α-benzyloxy-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-ene 15. Ketone *rac*-**3** (8.83 g, 34.2 mol), dry NH_4OAc (26.3 g, 342 mmol) and $NaBH_3CN$ (1.50 g, 24.0 mmol) in dry MeOH (100 ml) was allowed to react as described for compound **14**. After removal of the solvent the crude product was dissolved in pyridine (7 ml) and DMAP (catal.) and benzoyl chloride (6 ml, 51 mmol) were added at 0°C. The mixture was stirred for 1 h at 0°C and for 8 h at rt. Then water and MTBE were added. The aqueous layer was extracted with MTBE (3×), the combined organic phase washed with 2N HCl, sat. aq. $NaHCO_3$ solution and dried ($MgSO_4$). After removal of the solvent the crude product was purified by chromatography (MTBE/CH) to afford **15** (10.43 g, 68%), colorless solid. IR (neat) ν 3460, 3064, 2974, 2930, 2872, 1715, 1658, 1515, 1484 sv; 1452, 1278, 1103, 1065, 950 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (m, 1H, *p*-Ar-H), 7.68 (m, 2H, *o*-Ar-H), 7.55 (m, 2H, *m*-Ar-H), 7.55–7.38 (m, 7H, Ar′-H), 6.89 (d, ^3J=7.9 Hz, 1H, N*H*COPh), 6.22 (d, ^3J=5.7 Hz, 1H, H-7), 6.18 (d, ^3J=5.7 Hz, 1H, H-6), 4.83 (dt, ^3J=6.7, 1.1 Hz, 1H, H-3), 4.56 (d, ^2J=11.3 Hz, 1H, OCH_2Ph), 4.36 (d, ^2J=11.3 Hz, 1H, OCH_2Ph), 3.72 (d, ^3J=6.7 Hz, 1H, H-2), 2.14 (dd, ^2J=14.7 Hz, ^3J=6.3 Hz, 1H, H-4ax), 2.01 (dd, ^2J=14.7 Hz, ^3J=1 Hz, 1H, H-4eq), 1.46 (s, 3H, CH_3), 1.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.93 (C, C═O), 139.74/134.73 (CH, C-6, C-7) 136.78 (C, Ar′-C), 134.38 (C, Ar-C), 132.69 (CH, *p*-Ar-C), 130.88/126.19 (CH, *o*-, *m*-Ar-C), 127.73/127.41 (CH, *o*-, *m*-Ar′-C), 127.85 (CH, *p*-Ar′-C), 85.11/84.03 (C, C-1, C-5), 77.36 (CH, C-2), 70.93 (CH_2, O*C*H_2Ph), 43.74 (CH, C-3), 38.55 (CH_2, C-4), 23.05 (CH_3, CH_3), 20.58 (CH_3, CH_3); MS (130°C) (*m*/*z*) (0.5, M^++1), 288 (4), 256 (7), 217 (2), 191 (11), 166 (4), 150 (4), 122 (34), 105 (100), 91 (7), 79 (11).

2.1.17. 7α-*N*-Benzoylamino-1,5-dimethyl-3,9-dioxatricyclo[3.3.1.0^{2,4}]nonan-6α-ol 16 and 4α-*N*-benzoylamino-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9β-ol 17. Amide **15** (720 mg, 1.98 mmol) and *m*-CPBA (900 mg, ~4 mmol, 70–75%) were allowed to react as described for compound **4a** to afford after chromatography (MTBE/CH) the epoxide (618 mg, 82%), white solid. IR (neat) ν 3433, 3043, 2976, 2931, 2872, 1807, 1668, 1510, 1480, 1453, 1256, 1098, 1063, 992, 887 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 2H, *o*-Ar-H), 7.52 (m, 1H, *p*-Ar-H), 7.42 (m, 2H, *m*-Ar-H), 7.31–7.24 (m, 5H, Ar-H), 4.58 (d, ^2J=11.3 Hz, 1H, OCH_2Ph), 4.49 (dt, ^3J=4.9, 1.6 Hz, 1H, H-3), 4.34 (d, ^2J=11.3 Hz, 1H, OCH_2Ph), 3.66 (d, ^3J=2.7 Hz, 1H, H-7), 3.65 (d, ^3J=5 Hz, 1H, H-2), 3.41 (d, ^3J=2.7 Hz, 1H, H-6), 2.37 (dd, ^2J=15.3 Hz, ^3J=1.4 Hz, 1H, H-4eq), 2.02 (dd, ^2J=15.3 Hz, ^3J=5.8 Hz, 1H, H-4ax), 1.44 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz,$CDCl_3$) δ 167.22 (C, C═O), 137.84 (CH, *p*-Ar-C), 136.56 (C, Ar′-C), 134.35 (C, Ar-C), 131.79/126.74 (CH, *o*-, *m*-Ar-C), 128.77/128.34 (CH, *o*-, *m*-Ar′-C), 128.60 (CH, *p*-Ar′-C), 78.82/77.43 (C, C-1, C-5), 77.05 (CH, C-2), 71.83 (CH_2, O*C*H_2Ph), 57.38/55.78 (CH, C-6, C-7) 44.38 (CH, C-3), 37.81 (CH_2, C-4), 19.82 (CH_3, CH_3), 17.63 (CH_3, CH_3); MS (130°C) (*m*/*z*) 380 (2, M^++1), 289 (3), 274 (3), 231 (4), 225 (2), 191 (12), 166 (3), 148 (12), 128 (11), 105 (100), 91 (29), 77 (22).

A mixture of the epoxide (540 mg, 1.42 mmol), AcOH (0.15 ml) and a catalytic amount of Pd/C in MeOH (7 ml) was hydrogenated for 1 d and then filtered through a short column to remove Pd/C. The column was washed with MeOH/MTBE. The filtrate was concentrated and then diluted with DCM. The organic phase was washed with aq. Na_2CO_3 solution (5%) (3×). The aqueous layer was extracted with DCM and the combined organic phase dried ($MgSO_4$) and evaporated. After removal of the solvent the crude product was chromatographed (MTBE) to give hydroxy epoxide **16** (200 mg, 49%) and oxetane **17** (60 mg, 13%), white solids. Data for **16**: IR (neat) ν 3260, 2978, 2933, 2873, 1643, 1634, 1516, 1445, 1365, 1223, 1186, 1090, 1062, 957, 889 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 2H, *o*-Ar-H), 7.49 (m, 1H, *p*-Ar-H), 7.41 (m, 2H, *m*-Ar-H), 6.67 (d, ^2J=5.4 Hz, N*H*CO), 4.29 (dt, ^3J=5.6, 1.5 Hz, 1H, H-3), 3.84 (d, ^3J=6.5 Hz, 1H, H-2), 3.69 (d, ^3J=2.9 Hz, 1H, H-7), 3.39 (d, ^3J=2.9 Hz, 1H, H-6), 2.14 (dd, ^2J=15.3 Hz, ^3J=1.5 Hz, 1H, H-4eq), 2.01 (dd, ^2J=15.3 Hz, ^3J=5.9 Hz, 1H, H-4ax), 1.44 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.21 (C, C═O), 135.73 (C, Ar-C), 133.79 (CH, *p*-Ar-C), 130.60/ 128.47 (CH, *o*-, *m*-Ar-C), 80.97/78.90 (C, C-1, C-5), 73.09 (CH, C-2), 59.02/57.43 (CH, C-6, C-7) 49.42 (CH, C-3), 38.69 (CH_2, C-4), 21.62 (CH_3, CH_3), 19.07 (CH_3, CH_3); MS (130°C) (*m*/*z*) 289 (4, M^+), 275 (4), 228 (3), 203 (5), 190 (8), 163 (7), 146 (15), 122 (16), 105 (100), 77 (26).

2.1.18. 4α-*N*-Benzoylamino-6,8-dimethyl-2,7-dioxatricyclo[4.2.1.0^{3,8}]nonan-9β-ol 17. To a solution of epoxy alcohol **16** (1.67 g, 5.78 mmol) in THF (50 ml) was added LiH (45.0 mg, 5.35 mmol) followed by KOBu^t (712 mg, 6.35 mmol) at 0°C. The resulting mixture was stirred for 16 h at rt, then sat. aq. NH_4Cl solution (10 ml) and MTBE were added. The aqueous layer was extracted with MTBE and the combined organic phase dried ($MgSO_4$) and evaporated. The crude product was chromatographed to afford **17** (300 mg, 18%), colorless solid. IR (neat) ν 3395, 2973, 2932, 1613, 1576, 1447, 1343, 1234, 1200, 1110, 1079, 937, 952, 700 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (m, 2H, *o*-Ar-H), 7.52 (m, 1H, *p*-Ar-H), 7.46 (m, 2H, *m*-Ar-H), 4.61 (d, ^3J=1.6 Hz, 1H, H-2), 4.57 (s, 1H, H-7), 4.29 (dt, ^3J=8.8, 1.6 Hz, 1H, H-3), 3.90 (s, 1H, H-6), 2.26 (ddd, ^2J=13.5 Hz, ^3J=8.8 Hz, ^4J=0.75 Hz, 1H, H-4eq), 1.96 (dd, ^2J=13.5 Hz, ^3J=10 Hz, 1H, H-4ax), 1.61 (s, 3H, CH_3), 1.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CD_3OD) δ 169.93 (C, C═O), 135.57 (C, Ar-C), 132.75 (CH, *p*-Ar-C), 129.52/128.47 (CH, *o*-, *m*-Ar-C), 96.07 (CH, C-2), 88.88 (CH, C-7), 85.09/82.49 (C, C-1, C-5), 81.70 (CH, C-6), 47.71 (CH, C-3), 35.49 (CH_2, C-4), 21.97/19.15 (CH_3, 2×CH_3); MS (130°C) (*m*/*z*) 289 (2, M^+), 273 (16), 243 (6), 198 (4), 186 (9), 177 (9), 150 (3), 121 (12), 105 (100), 77 (26). For X-ray crystal structure see Ref. 12.

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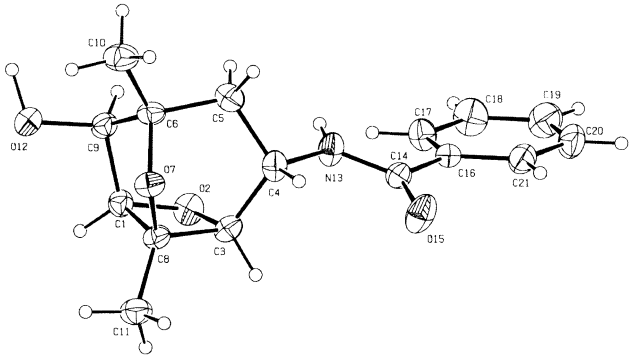
12. X-Ray crystal structures of **9b** and **17** (relative configuration): crystal structure data (without structure factors) of **9b**, **17** and **16** were deposited in Cambridge, No. CCDC 174 538, CCDC 174 540, CCDC 174 539, respectively.



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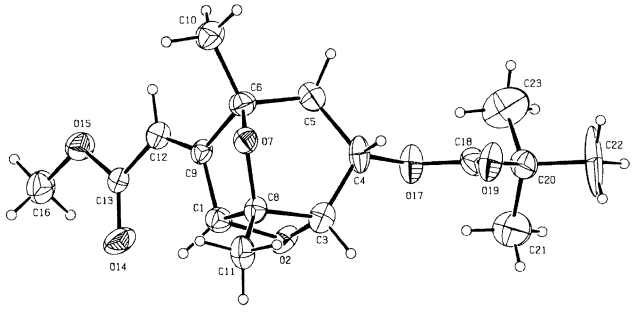

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