Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2999–3009

TETRAHEDRON:
ASYMMETRY

Synthesis of a highly functionalized γ-lactone as a precursor of 9-pentyl anthracyclines

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Received 17 June 1998; accepted 7 August 1998

Abstract

The synthesis of non racemic chiral γ-lactone **7** from α-D-isosaccharino-1,4-lactone (+)-**8**, as a precursor of the A-ring of the targeted 3′-morpholinyl-9-pentyl anthracycline **6**, is described. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

The anthracycline antibiotics daunorubicin **1** and doxorubicin **2** are of primary importance in cancer chemotherapy.[1] In particular, doxorubicin has been used successfully to produce regression in disseminated neoplastic diseases such as breast carcinoma, malignant lymphoma and sarcomas. The clinical value of anthracyclines is limited by the development of multidrug resistance (MDR)[1,2] which may be due to one or several mechanisms, most notably P-glycoprotein (PGP) associated multidrug resistance (MDR1) and alterations in topoisomerase II. One strategy to overcome this drawback is the classic analogue development[3,4] through structure–activity studies. In the case of doxorubicin and aclacinomycin analogues, Coley et al.[5] have evaluated 9-alkyl-modified anthracyclines on MDR cell lines on the basis of P-glycoprotein overproduction and overexpression of the MDR1 gene, and were successful at addressing the circumvention of multidrug resistance, most notably the 9-ethyl R_0 31-1966 **3** and 13-methyl aclacinomycin **4** (Fig. 1). This work showed a significant correlation between lipophilicity and MDR-reversing ability, where lipophilic 9-alkyl groups are believed to increase the rate of cellular uptake. It is noteworthy that other elements may be involved in the effectiveness of these compounds, such as affinity for the membrane efflux pump PGP, intracellular distribution, endocytosis, and membrane trafficking. Moreover, studies[6] on morpholinyl anthracyclines have disclosed the essential role of the intramolecular combination of 9-alkyl substitution and the 3′-morpholinyl ring to obtain resistance factors (RF) close to unity, and have confirmed the identification[7] of MX2 **5** as a promising antitumour agent.[8] Additional

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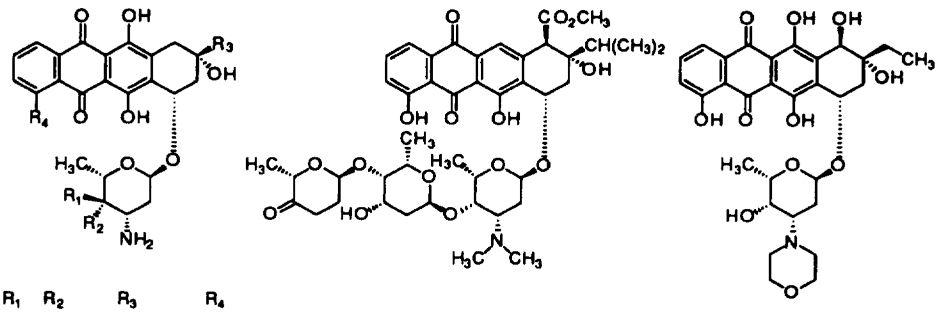
PII: S0957-4166(98)00320-6



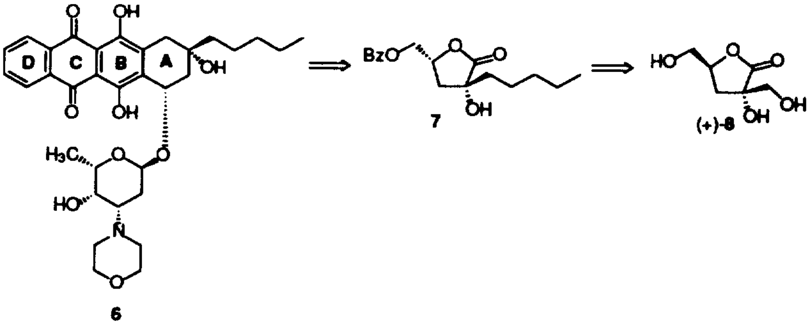
	R_1	R_2	R_3	R_4
1	H	OH	$COCH_3$	OCH_3
2	H	OH	$COCH_2OH$	OCH_3
3	OH	H	CH_2CH_3	H

4 **5**

Fig. 1.

lipophilicity of the morpholinyl sugar unit would not be the only determinant favouring retention of activity in P-glycoprotein-overexpressing MDR cells, indeed its enzymatic activation might lead to DNA alkylation.[9]

As part of our program[10] aimed at the reversal of anthracycline resistance, we have reported[11] the synthesis and activity of a 4′-morpholino-9-methyl anthracycline demonstrating that the morpholino substitution in the sugar moiety is amenable at the C-4′ position, but this appears to be of minor importance from the observations reported by the Farmitalia group.[3] It was of interest to undertake the synthesis of the 3′-morpholinyl-9-pentyl anthracycline **6** potentially endowed with higher lipophilic property than the mentioned derivatives. In this account, we describe the synthesis of chiral 4-benzoyloxymethyl-2-hydroxy-2-pentyl γ-lactone **7** from the readily available α-D-isosaccharino-1,4-lactone **8**,[12] which is a key intermediate of our target compound **6** utilizing a strategy based upon aldol methodology **A+BCD** as shown in the retrosynthetic analysis (Scheme 1).

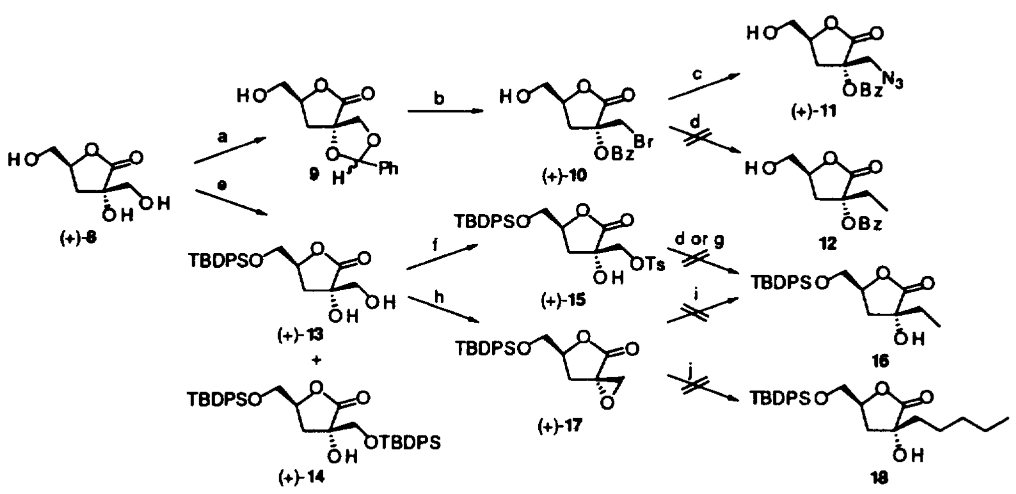


Scheme 1.

2. Results and discussion

We first tried to construct[13] the chiral tertiary hydroxy group of **3** and **5** in order to evaluate the reactivity of the γ-lactone substrates such as **10**, **15**, and **17**, prepared from **8**, vis-à-vis substitution reactions (Scheme 2).

Lactone **8** was converted into benzylidene **9** (PhCHO, $ZnCl_2$, rt) as a 1:2 mixture of *endo*- and *exo*-diastereoisomers in 88% overall yield. Several attempts[14] were made to achieve this protection. Benzylidene acetal opening via the procedure of Hanessian[15] (NBS, C_6H_6, $NaHCO_3$, 80°C) delivered

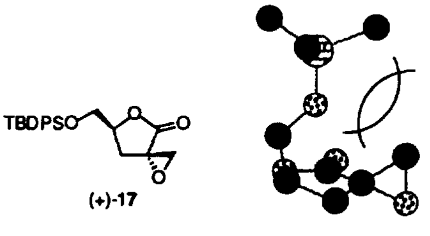


Reagents and Conditions: a) PhCHO, $ZnCl_2$, 25 °C (88%); b) NBS, $(PhCO)_2O_2$ C_6H_6, 80 °C (66%); c) LiN_3, DMF, 70 °C (60%); d) MeMgI, $CuBr-SMe_2$, THF, -78 °C ---> 0 °C; e) TBDPSCl, imidazole, DMF, 25 °C, 13 (76%) and 14 (11%); f) TsCl, Et_3N, CH_2Cl_2, 25 °C (43%); g) Me_2CuLi, THF, -20 °C; h) DEAD, PPh_3, C_6H_6, 4 Å m.s., reflux (85%); i) $Me_2Cu(CN)Li_2$, THF, -78 °C ---> 0 °C or $Me_2Cu(CN)Li_2$, BF_3-Et_2O, THF, -78 °C ---> 0 °C; j) $Bu_2Cu(CN)Li_2$, THF, -78 °C ---> -20 °C.

Scheme 2.

bromo-lactone (+)-**10** in 59% yield but the yield was improved to reach 66% in the presence of benzoyl peroxide as the catalyst.[16] We next examined nucleophilic displacements of the neopentyl bromide **10**. Azidolysis (LiN_3, DMF, 70°C) afforded the azido lactone (+)-**11** in 60% yield, which could serve as a useful chiron for the preparation of SM-5887[17] analogues wherein the A-ring contains an amino group at the C-13 position. In contrast with the azide ion, introduction of the methyl group (MeMgI, $CuBr-SMe_2$, THF)[18] was not effective. We then sought to prepare the tosylate derivative **15**. Protection of the neopentyl alcohol of (+)-**8** as the TBDPS ether (TBDPSCl, imidazole, DMF, rt) gave the lactone (+)-**13** in 76% yield, along with a minor amount of the corresponding bis-silyl lactone (+)-**14** (11%). Tosylation of **13** (TsCl, Et_3N, CH_2Cl_2, rt) then furnished (+)-**15** in 43% yield. Attempts to displace tosylate via copper-catalyzed Grignard reaction (MeMgI, $CuBr-SMe_2$, THF) or cuprate reaction[19] (Me_2CuLi, THF, −20°C) were unsuccessful. Finally, we also briefly examined the possibility of forming carbon–carbon bonds from spiroepoxy γ-lactone **17**.[20] To this end, treatment of (+)-**13** according to the Mitsunobu protocol[21] provided the desired epoxy lactone (+)-**17** in 85% yield. However, we were unable to achieve nucleophilic opening of epoxide (+)-**17** by the higher order cuprate $Me_2Cu(CN)Li_2$[22] or $Me_2Cu(CN)Li_2/BF_3$–Et_2O.[23] Importantly, reaction of **17** with $Bu_2Cu(CN)Li_2$ was attempted to obtain **18** but also failed. As we anticipated, the lack of substitution reaction presumably comes from the sterically congested transition state due to the neopentylic systems[24] and an unfavourable specific conformation[25] towards the attack of an organometallic species from the β-face. Molecular modelling (*Chem 3D Pro*, MM2 force field, dihedral driver, molecular dynamics) provided a possible minimum conformation for **17** (TBDPS modelled as TMS group). This model revealed high steric bias due to the close proximity of the TMS group and the C_2 centre of the epoxide moiety ($d(O$–$C_2)=3.23$ Å) which should not lead to β-face attack (Fig. 2). In addition, in the case of **10** and **15**, the S_N2 mechanism is currently known to be retarded by proximal electron-withdrawing groups.[26]

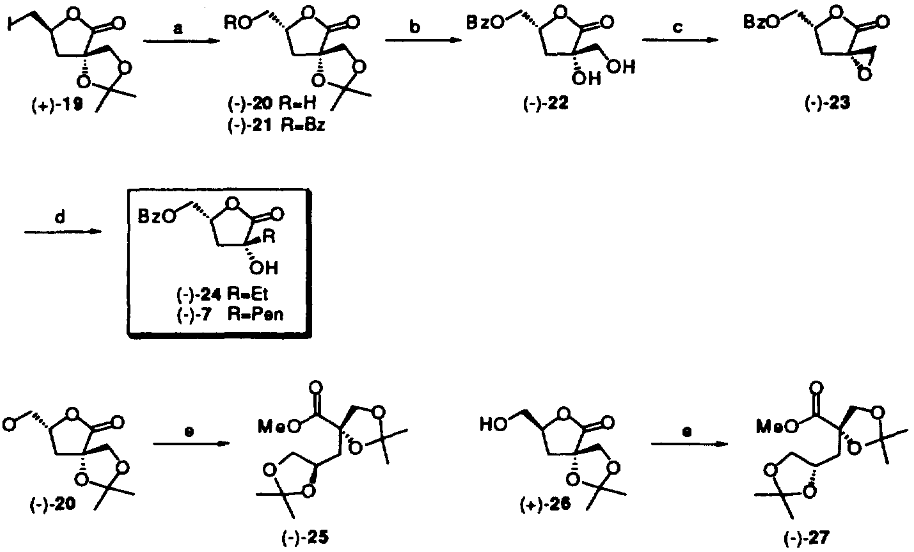
As an alternative, we decided to examine the ring expansion of the known iodo-lactone (+)-**19**[27] based on the methodology developed by Shibata et al.[28] in order to investigate the feasibility of the nucleophilic ring opening of a spiroepoxy δ-lactone system. Unexpectedly, treatment of (+)-**19** with



Conformation for 17

Fig. 2.

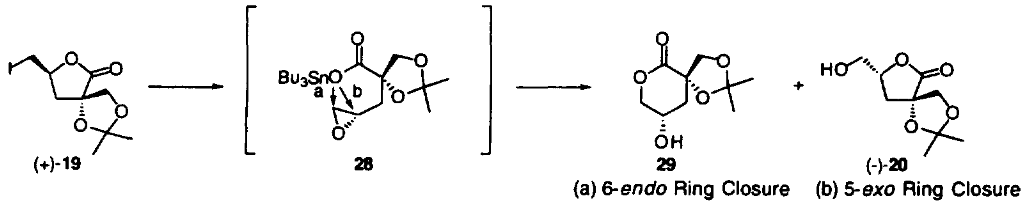
$(Bu_3Sn)_2O$ provided γ-lactone (−)-**20** in 47% yield (Scheme 3). The structure and the stereochemical assignment were based on spectroscopic analysis (IR, ^1H NMR, MS) and comparison with the α-D-isosaccharino-1,4-lactone derivative (+)-**26**.[29] The diastereoisomeric relationship was also confirmed by comparison (IR, ^1H NMR, MS) of esters **25** (52%) and **27**[30] prepared from γ-lactone **20** and epimeric γ-lactone **26**, respectively.



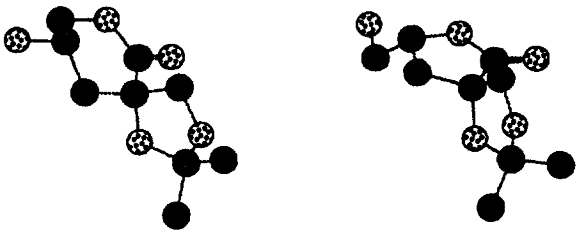
Reagents and Conditions: a) $(Bu_3Sn)_2O$, 80 °C, **20** (47%) or $(Bu_3Sn)_2O$, 80 °C then BzCl, pyridine-CH_2Cl_2 (1:9), 25 °C, **21** (46%, 2 steps); b) CF_3CO_2H, CH_2Cl_2-H_2O (10:1), 0 °C (quant.); c) DEAD, PPh_3, C_6H_6, 4 Å m.s., reflux (92%); d) $Me_2Cu(CN)Li_2$, THF, -78 °C, **24** (52%) or $Bu_2Cu(CN)Li_2$, THF, -78 °C ---> -20 °C, **7** (50%); e) α,α-DMP, Amberlyst 15, MeOH, 25 °C, **25** (52%) and **27** (ref. 30).

Scheme 3.

We speculate that the inversion of the C_7 stereocentre in this reaction is established through the epoxide intermediate **28** giving rise to **20** by 5-*exo* ring closure[31] as generally observed[32] (Scheme 4).



Scheme 4.



δ-Lactone **29**
$\Delta H°_{for}$ = -218.02 Kcal/mol

γ-Lactone **20**
$\Delta H°_{for}$ = -222.09 Kcal/mol

Fig. 3.

The formation of the γ-lactone (−)-**20** is also understandable on the basis of calculated heats of formation of **20** and δ-lactone **29** (6-*endo* ring closure). They were calculated using the AM1 method (*Chem 3D Pro*, MOPAC) (Fig. 3). The γ-lactone **20** is more stable (4.07 kcal/mol) than the δ-lactone **29**.

For larger scale, we prepared directly γ-lactone (−)-**21** in 46% yield (2 steps). Acidic hydrolysis of **21** and epoxidation of **22** gave the spiroepoxy γ-lactone (−)-**23**. Molecular mechanics minimization of the geometry of **23** showed a possible conformation[33] which would serve to direct approaching nucleophiles to β-face. To our delight, the reaction of $Me_2Cu(CN)Li_2$ and $Bu_2Cu(CN)Li_2$ afforded (−)-**24** and the suitable γ-lactone (−)-**7** in 52% and 50% yields, respectively.

In summary, the synthesis of (−)-**7** as an A-ring precursor of 3′-morpholinyl-9-pentyl anthracycline **6** reveals the continuing pivotal role of α-D-isosaccharino-1,4-lactone **8** in anthracycline chemistry.

3. Experimental

3.1. General procedures

^{1}H NMR spectra were recorded on Bruker AM-200, 250 and 270 instruments. IR spectra were recorded on a Perkin–Elmer 1710 infrared spectrophotometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Melting points were determined on either a Kofler hot-stage instrument or an electrothermal digital melting point apparatus and are not corrected. Mass spectra (MS) were registered on a Nermag R10-10C mass spectrometer under chemical ionization (CI) conditions. Elemental analyses were performed by the 'Service d'Analyse du CNRS, Vernaison, France'. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light and 20% methanolic sulfuric acid, heat was used as a developing agent. E. Merck silica gel (particle size 0.040–0.063 mm) was used for flash column chromatography.[34] All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated.

3.2. (5S,8S)-8-Hydroxymethyl-2-phenyl-1,3,7-trioxaspiro[4.4]nonan-6-one 9

To a solution of lactone **8** (200 mg, 1.23 mmol) in benzaldehyde (4 mL) was added dry zinc chloride (195 mg, 1.43 mmol). The mixture was stirred for 1.5 h at room temperature and then diluted with ethyl acetate. The ethyl acetate extracts were washed successively with saturated aqueous $NaHCO_3$ and water, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane:acetone (8:1) as eluent, afforded a separable mixture of two diastereoisomeric forms of **9** in a 2:1 ratio (265 mg, 88%

overall yield). The major compound was an oil: $[\alpha]_D^{22}$=+47 (*c* 0.8, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.55 (m, 2H, aryl), 7.40 (m, 3H, aryl), 5.90 (s, 1H, H-2), 4.72 (m, 1H, H-8), 4.60 (d, *J*=9.5 Hz, 1H, H-4), 4.02 (d, *J*=9.5 Hz, 1H, H-4), 4.00 (dd, *J*=12.7, 2.5 Hz, 1H, H-10), 3.60 (dd, *J*=12.7, 3 Hz, 1H, H-10), 2.91 (s, 1H, OH), 2.59 (dd, *J*=13.9, 7.3 Hz, 1H, H-9), 2.35 (dd, *J*=13.9, 6.7 Hz, 1H, H-9). MS (DCI, NH_3) *m/e* 251 $[M+H]^+$, 268 $[M+NH_4]^+$.

The minor compound was a solid: mp 72–74°C. $[\alpha]_D^{22}$=+55.1 (*c* 0.8, $CHCl_3$). IR ($CDCl_3$): 3606, 3471, 2949, 2887, 1778, 1607 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.50 (m, 2H, aryl), 7.30 (m, 3H, aryl), 6.07 (s, 1H, H-2), 4.75 (m, 1H, H-8), 4.37 (d, *J*=8.9 Hz, 1H, H-4), 4.30 (dd, *J*=8.9 Hz, 1H, H-4), 4.00 (dd, *J*=12.8, 2.5 Hz, 1H, H-10), 3.60 (dd, *J*=12.8, 3 Hz, 1H, H-10), 2.91 (bs, 1H, OH), 2.58 (dd, *J*=14, 7.5 Hz, 1H, H-9), 2.47 (dd, *J*=14, 6.4 Hz, 1H, H-9). MS (DCI, NH_3) *m/e* 251 $[M+H]^+$, 268 $[M+NH_4]^+$. Anal. calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.63. Found: C, 62.58; H, 5.62.

3.3. *(3S,5S)-3-Benzoyloxy-3-bromomethyl-5-hydroxymethyl-2-oxotetrahydrofuran* **10**

To a solution of **9** (220 mg, 0.88 mmol) in benzene (20 mL) were added *N*-bromosuccinimide (180 mg, 1.01 mmol) and a few granules of benzoyl peroxide. The resultant mixture was heated to reflux for 1.5 h. The mixture was then diluted with ethyl acetate, washed with saturated aqueous $NaHCO_3$, saturated $Na_2S_2O_3$ and brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane:ethyl acetate (3:1) as eluent, gave 193 mg (66%) of **10** as a solid: mp 89–91°C. $[\alpha]_D^{22}$=+34.8 (*c* 0.79, $CHCl_3$). IR ($CDCl_3$): 3477, 3073, 2962, 2879, 1780, 1724, 1602 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.05 (dd, *J*=7.5, 1.5 Hz, 2H, aryl), 7.60 (t, *J*=7.5 Hz, 1H, aryl), 7.45 (m, 2H, aryl), 5.05 (m, 1H, H-5), 4.06 (dd, *J*=13.5, 2.5 Hz, 1H, H-6), 3.95 (d, *J*=10.5 Hz, 1H, H-3′), 3.86 (d, *J*=10.5 Hz, 1H, H-3′), 3.70 (dd, *J*=13.3, 3 Hz, 1H, H-6), 2.75 (dd, *J*=14.5, 6 Hz, 1H, H-4), 2.60 (dd, *J*=14.5, 8.5 Hz, 1H, H-4), 2.53 (s, 1H, OH). MS (DCI, NH_3) *m/e* 329 ($[M+H]^+$, ^{79}Br), 331 ($[M+H]^+$, ^{81}Br), 346 ($[M+NH_4]^+$, ^{79}Br), 348 ($[M+NH_4]^+$, ^{81}Br). Anal. calcd for $C_{13}H_{13}O_5Br$: C, 47.43; H, 3.98. Found: C, 47.64; H, 4.01.

3.4. *(3S,5S)-3-Azidomethyl-3-benzoyloxy-5-hydroxymethyl-2-oxotetrahydrofuran* **11**

To a solution of **10** (100 mg, 0.30 mmol) in DMF (15 mL) was added LiN_3 (38 mg, 0.76 mmol). After 3.5 h at 70°C, the mixture was diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane:ethyl acetate (2:1) as eluent, provided 53 mg (60%) of **11** as a solid: mp 113–115°C. $[\alpha]_D^{22}$=+88.7 (*c* 0.8, $CHCl_3$). IR ($CDCl_3$): 3628, 2934, 2108, 1779, 1723, 1602 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.08 (dd, *J*=8, 1.5 Hz, 2H, aryl), 7.66 (t, *J*=8 Hz, 1H, aryl), 7.50 (dd, *J*=8 Hz, 2H, aryl), 5.05 (m, 1H, H-5), 4.08 (dd, *J*=12, 2 Hz, 1H, H-6), 3.97 (d, *J*=13 Hz, 1H, H-3′), 3.70 (dd, *J*=12, 3 Hz, 1H, H-6), 3.68 (d, *J*=13 Hz, 1H, H-3′), 2.70 (dd, *J*=15, 6 Hz, 1H, H-4), 2.60 (dd, *J*=15, 9 Hz, 1H, H-4), 2.10 (s, 1H, OH). MS (DCI, NH_3) *m/e* 292 $[M+H]^+$, 309 $[M+NH_4]^+$.

3.5. *(3S,5S,)-5-(*tert*-Butyldiphenylsilyloxy)methyl-3-hydroxy-3-hydroxymethyl-2-oxotetrahydrofuran* **13** *and (3S,5S)-3,5-di-(*tert*-butyldiphenylsilyloxy)methyl-3-hydroxy-2-oxotetrahydrofuran* **14**

To a solution of **8** (2 g, 12.5 mmol) in DMF (10 mL) were added imidazole (42 mg, 0.62 mmol) and *tert*-butyldiphenylsilyl chloride (3.2 mL, 12.6 mmol). The solution was stirred at room temperature for 2 h before being diluted with H_2O. The mixture was extracted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane:ethyl acetate (3:1) as eluent, furnished 3.8 g (76%) of **13** as a solid and 900 mg (11%) of **14** as an oil.

Compound **13**: mp 106–107°C. $[\alpha]_D^{22}$=+37.5 (*c* 0.81, $CHCl_3$). IR ($CDCl_3$): 3537, 3450, 3075, 1767 cm^{-1}. ^1H NMR (200 MHz, CD_3COCD_3) δ 7.72 (m, 4H, aryl), 7.44 (m, 6H, aryl), 4.90 (s, 1H, OH), 4.75 (m, 1H, H-5), 4.13 (dd, *J*=6.3, 5.1 Hz, 1H, OH), 3.92 (dd, *J*=11.5, 3.4 Hz, 1H, H-6), 3.78 (dd, *J*=11.5, 5.4 Hz, 1H, H-6), 3.74 (dd, *J*=10.5, 6.3 Hz, 1H, H-3′), 3.59 (dd, *J*=10.7, 5.1 Hz, 1H, H-3′), 2.52 (dd, *J*=13.6, 9 Hz, 1H, H-4), 2.13 (dd, *J*=13.6, 6.5 Hz, 1H, H-4), 1.10 (s, 9H, $C(CH_3)_3$). MS (DCI, NH_3) *m/e* 418 $[M+NH_4]^+$. Anal. calcd for $C_{22}H_{28}O_5Si$: C, 66.97; H, 7.04. Found: C, 67.16; H, 7.07.

Compound **14**: $[\alpha]_D^{22}$=+16.2 (*c* 0.81, $CHCl_3$). IR ($CDCl_3$): 3674, 3563, 3074, 2956, 1780, 1590 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.75 (m, 5H, aryl), 7.45 (m, 15H, aryl), 4.80 (m, 1H, H-5), 3.87 (dd, *J*=10, 4 Hz, 1H, H-6), 3.83 (d, *J*=10 Hz, 1H, H-3′), 3.77 (dd, *J*=10, 3.4 Hz, 1H, H-6), 3.74 (d, *J*=10 Hz, 1H, H-3′), 3.07 (s, 1H, OH), 2.37 (dd, *J*=14, 8 Hz, 1H, H-4), 2.30 (dd, *J*=14, 7.5 Hz, 1H, H-4), 1.15 (s, 9H, $C(CH_3)_3$), 1.10 (s, 9H, $C(CH_3)_3$). MS (DCI, NH_3) *m/e* 656 $[M+NH_4]^+$.

*3.6. (3*S*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)methyl-3-hydroxy-2-oxo-3-(*para*-toluenesulfonyl-oxy) methyltetrahydrofuran 15*

To a solution of **13** (500 mg, 1.25 mmol) in methylene chloride (30 mL) were added *p*-toluenesulfonyl chloride (248 mg, 1.3 mmol) and triethylamine (180 μL, 1.3 mmol). The solution was stirred at room temperature for 16 h. At the end of this time, the mixture was diluted with ethyl acetate, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Flash chromatography, with cyclohexane:ethyl acetate (4:1) as eluent, gave 300 mg (43%) of tosylate **15** as an oil: $[\alpha]_D^{22}$=+17.5 (*c* 0.79, $CHCl_3$). IR ($CDCl_3$): 3457, 3073, 2932, 2860, 1778, 1600 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.80 (d, *J*=7.5 Hz, 2H, aryl), 7.60 (m, 4H, aryl), 7.45 (m, 6H, aryl), 7.35 (d, *J*=7.5 Hz, 2H, aryl), 4.75 (m, 1H, H-5), 4.23 (d, *J*=10 Hz, 1H, H-3′), 4.14 (d, *J*=10 Hz, 1H, H-3′), 3.94 (dd, *J*=12, 3.5 Hz, 1H, H-6), 3.74 (dd, *J*=12, 4 Hz, 1H, H-6), 2.92 (s, 1H, OH), 2.50 (m, 4H, H-4 and CH_3), 2.32 (dd, *J*=14, 7 Hz, 1H, H-4), 1.10 (s, 9H, $C(CH_3)_3$). MS (DCI, NH_3) *m/e* 572 $[M+NH_4]^+$.

*3.7. (3*S*,6*S*)-6-(*tert*-Butyldiphenylsilyloxy)methyl-1,5-dioxaspiro[2.4]heptan-4-one 17*

To a solution of diol **13** (1.9 g, 4.75 mmol) in benzene (50 mL) were added successively 4 Å molecular sieves (1.9 g), PPh_3 (1.37 g, 5.23 mmol) and DEAD (860 μL, 5.46 mmol). After 3 h at reflux, the reaction mixture was filtered, and the filtrate was diluted with ether. The organic solution was washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Following concentration *in vacuo*, the residue was purified by flash chromatography, with cyclohexane:ethyl acetate (5:1) as eluent, to provide 1.55 g (85%) of epoxide **17** as a solid: mp 72–73°C. $[\alpha]_D^{22}$=+44.5 (*c* 0.81, $CHCl_3$). IR ($CDCl_3$): 3074, 2962, 2933, 2861, 1790, 1590 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.70 (dd, *J*=7, 1.5 Hz, 4H, aryl), 7.45 (m, 6H, aryl), 4.85 (m, 1H, H-6), 4.04 (dd, *J*=11.5, 3 Hz, 1H, H-8), 3.75 (dd, *J*=11.5, 2.5 Hz, 1H, H-8), 3.28 (d, *J*=6 Hz, 1H, H-2), 3.09 (d, *J*=6 Hz, 1H, H-2), 2.65 (dd, *J*=14, 9 Hz, 1H, H-7), 2.55 (dd, *J*=14, 4 Hz, 1H, H-7), 1.10 (s, 9H, $C(CH_3)_3$). HRMS (DCI, CH_4) calcd for $C_{22}H_{27}O_4Si$ $(M+H)^+$: 383.1679. Found: 383.1677.

*3.8. (5*S*,8*R*)-8-Hydroxymethyl-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonan-6-one 20*

A solution of **19** (970 mg, 3.11 mmol) in bis(tributyltin) oxide (1.6 mL) was heated to 80°C for 2 h and then quenched by addition of methanol. Repeated flash chromatography, with cyclohexane:ethyl acetate (4:1 then 3:1) as eluent, furnished 296 mg (47%) of γ-lactone **20** as an oil: $[\alpha]_D^{22}=-30.6$ (*c* 0.81, $CHCl_3$). IR ($CDCl_3$): 3598, 2993, 1785, 1670 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.49 (m, 1H, H-8), 4.22 (d, *J*=8.6 Hz, 1H, H-4), 4.08 (d, *J*=8.6 Hz, 1H, H-4), 3.91 (dd, *J*=12.6, 2.9 Hz, 1H, H-10), 3.71 (d, *J*=12.6, 5.3 Hz, 1H, H-10), 3.70 (d, *J*=7.6 Hz, 1H, H-9), 2.02 (m, 1H, OH), 1.54 (s, 3H, Me), 1.47 (s, 3H, Me). MS (DCI, NH_3) *m/e* 203 $[M+H]^+$, 220 $[M+NH_4]^+$. Anal. calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.41; H, 7.01.

3.9. (5S,8R)-8-Benzoyloxymethyl-2,2-dimethyl-1,3,7-trioxaspiro[4.4]nonan-6-one 21

A solution of **19** (4 g, 13 mmol) in bis(tributyltin) oxide (7 mL) was heated to 80°C. After 6 h, benzoyl chloride (1.5 mL, 13 mmol) and a mixture of methylene chloride:pyridine (9:1) were added at room temperature. The resultant mixture was stirred for 24 h at room temperature, quenched by the addition of methanol (2 mL) and concentrated *in vacuo*. Flash chromatography, with cyclohexane:ethyl acetate (5:1) as eluent, followed by recrystallization with cyclohexane, gave 1.81 g (46%) of **21** as a solid: mp 94°C. $[\alpha]_D^{22}=-50$ (*c* 0.82, MeOH). IR (KBr): 3060, 1770, 1719, 1601 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 8.10 (d, *J*=7 Hz, 2H, aryl), 7.60 (m, 1H, aryl), 7.50 (m, 2H, aryl), 4.78 (m, 1H, H-8), 4.62 (dd, *J*=12, 3.4 Hz, 1H, H-10), 4.52 (dd, *J*=12, 6 Hz, 1H, H-10), 4.29 (d, *J*=9 Hz, 1H, H-4), 4.11 (d, *J*=9 Hz, 1H, H-4), 2.55 (dd, *J*=14.7 Hz, 1H, H-9), 2.40 (dd, *J*=14, 8 Hz, 1H, H-9), 1.60 (s, 3H, CH_3), 1.50 (s, 3H, CH_3). MS (DCI, NH_3) *m/e* 307 $[M+H]^+$, 324 $[M+NH_4]^+$. Anal. calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.88; H, 5.89.

3.10. (3S,5R)-5-Benzoyloxymethyl-3-hydroxy-3-hydroxymethyl-2-oxotetrahydrofuran 22

Trifluoroacetic acid (9 mL) and water (1 mL) were added to a solution of **21** (1 g, 3.27 mmol) in methylene chloride (10 mL) at 0°C. The reaction mixture was stirred for 1.5 h at 0°C, then diluted with toluene, and concentrated *in vacuo*. Flash chromatography, with cyclohexane:ethyl acetate (2:1) as eluent, afforded **22** (quant.): mp 101–102°C. $[\alpha]_D^{22}=-45.5$ (*c* 0.79, MeOH). IR (KBr): 3405, 3069, 1746, 1719, 1601 cm^{-1}. ^1H NMR (270 MHz, CD_3COCD_3) δ 8.00 (dd, *J*=7.5 Hz, 2H, aryl), 7.55 (m, 1H, aryl), 7.40 (m, 2H, aryl), 4.80 (m, 1H, H-5), 4.52 (dd, *J*=12, 3 Hz, 1H, H-6), 4.38 (dd, *J*=12, 6 Hz, 1H, H-6), 3.74 (d, *J*=10.5 Hz, 1H, H-3′), 3.62 (d, *J*=10.5 Hz, 1H, H-3′), 2.77 (s, 1H, OH), 2.72 (s, 1H, OH), 2.70 (dd, *J*=13, 7 Hz, 1H, H-4), 2.14 (dd, *J*=13, 7 Hz, 1H, H-4). MS (DCI, NH_3) *m/e* 267 $[M+H]^+$, 284 $[M+NH_4]^+$.

3.11. (3S,6R)-6-Benzoyloxymethyl-1,5-dioxaspiro[2.4]heptan-4-one 23

To a solution of diol **22** (332 mg, 1.25 mmol) in benzene (12 mL) were added successively 4 Å molecular sieves (332 mg), PPh_3 (358 mg, 1.36 mmol) and DEAD (232 μL, 1.47 mmol). After 25 min at reflux, the reaction mixture was diluted with ethyl acetate, washed with 5% aqueous HCl, saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Following concentration *in vacuo*, the residue was purified by flash chromatography, with cyclohexane:ethyl acetate (2:1) as eluent, to provide 285 mg (92%) of **23** as a solid: mp 81°C. $[\alpha]_D^{22}=-28.5$ (*c* 0.81, $CHCl_3$). IR ($CDCl_3$): 2952, 1795, 1724, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (m, 2H, aryl), 7.59 (m, 1H, aryl), 7.46 (m, 2H, aryl), 5.03 (m, 1H, H-6), 4.67 (dd, *J*=12.4, 2.8 Hz, 1H, H-8), 4.52 (dd, *J*=12.4, 4.5 Hz, 1H, H-8), 3.31 (d, *J*=6 Hz, 1H, H-2), 3.14 (d, *J*=6 Hz, 1H, H-2), 2.74 (dd, *J*=14.3, 7.8 Hz, 1H, H-7), 2.44 (dd, *J*=14.3, 6.6 Hz, 1H, H-7). HRMS (DCI, CH_4) calcd for $C_{13}H_{13}O_5$ $(M+H)^+$: 249.0763. Found: 249.0769.

3.12. *(3R,5R)-5-Benzoyloxymethyl-3-ethyl-3-hydroxy-2-oxotetrahydrofuran 24*

The cuprate $Me_2Cu(CN)Li_2$ was prepared from CuCN (23.4 mg, 0.261 mmol) in THF (1 mL), to which was added 1.0 M MeLi (522 mL, 0.522 mmol) at −78°C and the resultant mixture was stirred at this temperature for 20 min. To this mixture was added the epoxy γ-lactone **23** (50 mg, 0.201 mmol). Stirring for 30 min was followed by quenching and extractive workup (ethyl acetate). Flash chromatography with methylene chloride:methanol (95:5) furnished 27.7 mg (52%) of **24** as an oil: $[\alpha]_D^{22}=-31$ (*c* 0.29, $CHCl_3$). IR ($CDCl_3$): 3566, 2977, 1781, 1723, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J*=7.8 Hz, 2H, aryl), 7.58 (t, *J*=7.3 Hz, 1H, aryl), 7.45 (t, *J*=7.7 Hz, 2H, aryl), 4.71 (m, 1H, H-5), 4.61 (dd, *J*=12.5, 2.8 Hz, 1H, H-6), 4.42 (dd, *J*=12.5, 6.5 Hz, 1H, H-6), 2.77 (s, 1H, OH), 2.50 (dd, *J*=13.3, 6.6 Hz, 1H, H-4), 2.21 (dd, *J*=13.3, 8.8 Hz, 1H, H-4), 1.82 (q, *J*=7.4 Hz, 2H, CH_2–CH_3), 1.05 (t, *J*=7.4 Hz, 3H, CH_2–CH_3). MS (DCI, NH_3) *m/e* 265 $[M+H]^+$, 282 $[M+NH_4]^+$.

3.13. *(3R,5R)-5-Benzoyloxymethyl-3-hydroxy-3-pentyl-2-oxotetrahydrofuran 7*

The cuprate $Bu_2Cu(CN)Li_2$ was prepared from CuCN (23.4 mg, 0.261 mmol) in THF (1 mL), to which was added 2.5 M BuLi (208 μL, 0.522 mmol) at −78°C. The heterogeneous mixture was allowed to warm up to 0°C and was then cooled once again to −78°C. The epoxy γ-lactone **23** (50 mg, 0.201 mmol) in THF (0.6 mL) was added at −78°C, stirred at that temperature for 10 min and gradually warmed to −20°C. Quenching, extractive workup (ethyl acetate) and flash chromatography with cyclohexane:ethyl acetate (4:1) as eluent, gave 31.1 mg (50%) of **7** as a solid: mp 58–60°C. $[\alpha]_D^{22}=-25$ (*c* 0.48, $CHCl_3$). IR ($CDCl_3$): 3567, 2935, 2862, 1781, 1723, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J*=7.5 Hz, 2H, aryl), 7.59 (t, *J*=7.4 Hz, 1H, aryl), 7.45 (t, *J*=7.6 Hz, 2H, aryl), 4.72 (m, 1H, H-5), 4.62 (dd, *J*=12.4, 3 Hz, 1H, H-6), 4.42 (dd, *J*=12.4, 6.6 Hz, 1H, H-6), 2.51 (dd, *J*=13.2, 6.6 Hz, 1H, H-4), 2.23 (dd, *J*=13.2, 8.8 Hz, 1H, H-4), 1.83–1.26 (m, 8H, alkyl), 0.90 (t, *J*=6.5 Hz, 3H, alkyl). MS (DCI, NH_3) *m/e* 307 $[M+H]^+$, 324 $[M+NH_4]^+$. Anal. calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.92; H, 7.25.

3.14. *3-Deoxy-2-C-(methoxycarbonyl)-1,2:4,5-bis-O-(1-methylethylidene)-D-*erythro*-pentitol 25*

To a solution of lactone **20** (100 mg, 0.49 mmol) in methanol (2 mL) were added α,α-dimethoxypropane (5 mL) and 178 mg of Amberlyst 15 ion-exchange resin. The mixture was stirred for 23 h at room temperature, then filtered on Celite, and concentrated *in vacuo*. Flash chromatography, with cyclohexane:ethyl acetate (7:1) as eluent provided 71.4 mg (52%) of **25** as a liquid: $[\alpha]_D^{22}=-2.5$ (*c* 1, $CHCl_3$). IR ($CDCl_3$): 2990, 2955, 1750, 1455 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 4.34 (d, *J*=9.1 Hz, 1H, H-1), 4.29 (m, 1H, H-4), 4.10 (d, *J*=9.1 Hz, 1H, H-1), 4.01 (dd, *J*=8, 5.6 Hz, 1H, H-5), 3.75 (s, 3H, CO_2Me), 3.50 (t, *J*=8 Hz, 1H, H-5), 2.15 (dd, *J*=14.5, 6.5 Hz, 1H, H-3), 2.04 (dd, *J*=14.5, 5.4 Hz, 1H, H-3), 1.43 (s, 6H, CH_3), 1.32 (s, 3H, CH_3). HRMS (DCI, CH_4) calcd for $C_{13}H_{23}O_6$ $(M+H)^+$: 275.1495. Found: 275.1475.

Acknowledgements

The authors thank Ms. Geneviève Flad for her excellent assistance in NMR spectroscopy. This work was financially supported by the Centre National de la Recherche Scientifique and the Institut Curie, Section Recherche, France. Thanks are also due to the referees for critical reading of the manuscript in its first version.

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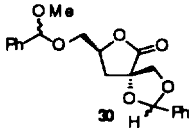

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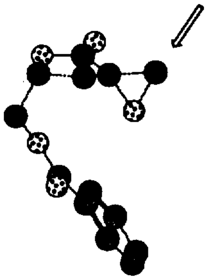
33. Molecular mechanics calculations (Chem 3D Pro, MM2 force field) find the following conformation related to **23**:



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