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Preparation of chiral 1,3 skipped *anti*- and *syn*-tetrols via highly enantioselective biocatalytic resolution

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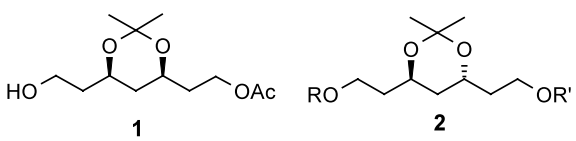
Abstract—Biocatalytic resolution of the 7-benzyloxy-3,5-*anti*-dioxolan-1,3,5,7-tetrol and the 7-benzyloxy-3,5-*syn*-dioxolan-1,3,5,7-tetrol was found to be highly enantioselective leading to differently functionalized chiral tetrols with significantly high e.e.

1. Introduction

Optically active 1,3-polyol units with *anti*- or *syn*-configuration are important fragments of the carbon framework of many natural products possessing potent biological and pharmacological activities. Examples include Macrolactine,[1] Bryostatins,[2] and the well known macrolide antibiotics Amphotericin B and Nystatin A_1,[3] which have been used clinically for the treatment of systemic fungal infections. The stereoselective synthesis of 1,3-skipped polyols has attained a level of considerable sophistication[4] and they are often prepared from stereodefined *anti*- or *syn*-1,3-diol subunits.

Previous reports from this laboratory have described the preparation of **1**[5] (see Fig. 1) by biocatalytic desymmetrization of the appropriate *meso*- precursor compound and the transformation of the resulting homochiral skipped 1,3-*syn*-tetrol into mevinic acid analogues[5b] as well as into the C(1)–C(10)[6] and C(1)–C(13)[7] fragments of the macrolide antibiotic Nystatin A_1.



1 **2**

Figure 1.

Since we need a new approach to the synthesis of polyol antibiotics, 1,3-tetrols of the type **2**, with an *anti*- relative configuration, we thought it may be possible to prepare the desired compound in optically active form by biocatalytic resolution, and eventually, to extend this approach to the analogous racemic 1,3-*syn*-tetrols.

2. Results and discussion

The racemic compounds to be resolved were easily prepared as shown in Scheme 1. The known β-hydroxy ketoester **3**[5] was reduced to 3,5-*anti*-diol **4** using $Me_4NBH(OAc)_3$[8] or to the corresponding 3,5-*syn*-diol using $Et_2BOMe/NaBH_4$.[9] Both reactions proceeded with excellent diastereoselection as has already been shown for these well known procedures.

The diols were then protected as acetonides and the ester groups were reduced to primary alcohols with $LiAlH_4$ to afford, (±)-**6** and (±)-**8**[10] and, after subsequent acylation, the corresponding acetates (±)-**7** and (±)-**9** in high overall yield.

Enzymatic resolution (Table 1) of the four racemic compounds was performed under transesterification conditions on the alcohols (±)-**6** and (±)-**8** (see Scheme 2) and under hydrolysis conditions on the respective (±)-**7** and (±)-**9** acetylated products (see Scheme 3), utilising the commercially available and inexpensive enzyme *Pseudomonas* sp. lipase (PSL, AMANO). The experiments were performed at different conversions and reaction times in order to optimise the enan-

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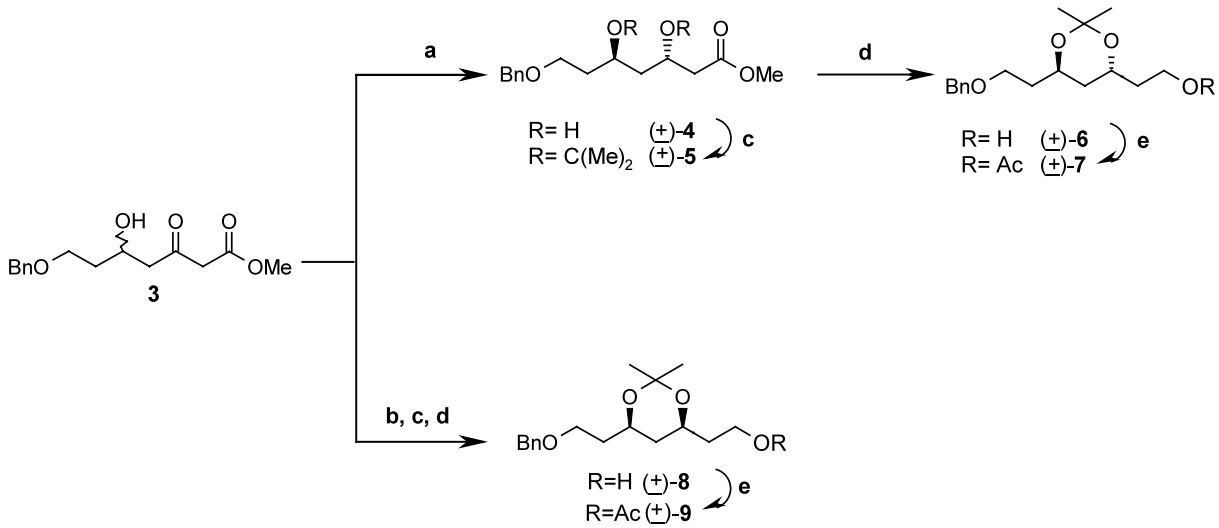
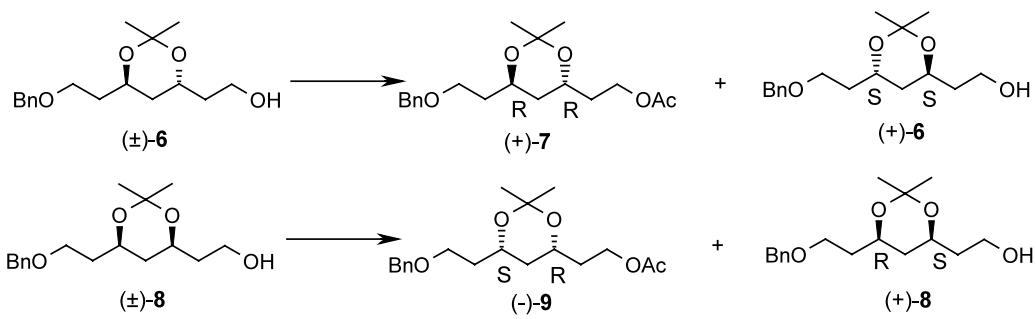


Scheme 1. Synthesis of the 1,3 skipped tetrols. (a) $Me_4NHB(OAc)_3$, $AcOH/CH_3CN$, –40°C, 18 h, 72%; (b) $Et_3B/MeOH$, $NaBH_4$, THF, –65°C, 90 min, 98%; (c) H^+, $(CH_3)_2C(OCH_3)_2$, rt, 24 h, 100%; (d) $LiAlH_4$, THF, rt, 30 min, 100%; (e) Ac_2O, DMAP, Et_3N, rt, 1.5 h, 90%.

Table 1. Enantioselective lipase catalysed reactions

Entry	Reaction			Products			Unreacted compounds			E^b
	Substrate	t (h)	Conversion (%)	Product	E.e.	$[\alpha]_D^a$	Substrate	E.e.	$[\alpha]_D^a$	
1	(±)-**6**	20	53	(+)-**7**	85	+0.66	(+)-**6**	98	+ 8.6	65
2	(±)-**8**	20	50	(−)-**9**	98	−1.31	(+)-**8**	98	+10.2	>100
3	(±)-**7**	11	36	(−)-**6**	98	−9.11	(−)-**7**	56[c]	–	>100
4	(±)-**9**	18	57	(−)-**8**	74	–	(+)-**9**	98	+1.3	30

[a] $CHCl_3$ as solvent, concentration ~1.0.
[b] See Ref. 11.
[c] $[\alpha]_D = -1.53$ from acetylation of (+)-**6**.

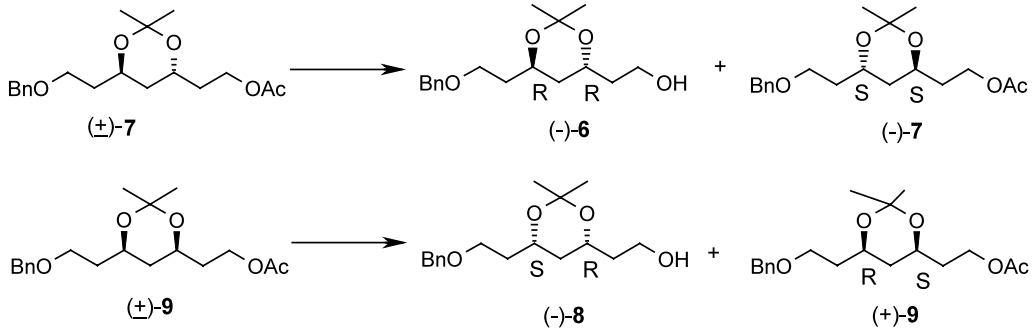


Scheme 2. Lipase-catalysed esterification.

tiomeric excess of the products and the enantiomeric ratio (E) which represents the ratio between the specific constant of the enzyme for the two competing enantiomers[11] (Table 1). This table shows the transesterification results of (±)-**6** and (±)-**8** in entries 1 and 2 and reports the hydrolysis results of (±)-**7** and (±)-**9** in entries 3 and 4.

The data (the e.e. values and the E values which exceed 30 in every case, normally considered as excellent) show indeed the exceptional ability of the enzyme for the enantiomeric discrimination of these substrates. This high selectivity in the biocatalytic resolution of substrates like compounds **1**[5] and **6**–**9**, is noteworthy because the stereogenic centres are two carbons away from the reaction centres. The high substrate affinity of this enzyme is probably related to the presence of the rigid acetonide ring[12] which fits well in the active site of the enzyme.

The enantiomeric excesses of the resolved compounds were evaluated by HPLC (compounds **6**, **7** and **8**) and by ^1H NMR analysis with chiral shift reagents (compound **9**) as described in Section 4.



Scheme 3. Lipase-catalysed hydrolysis.

The absolute configuration of compounds **6** and **7** have been determined on compound (+)-**7**, obtained in homochiral form after esterification of (−)-**6**, using a new general method[13] suitable for non-chromophoric alkyl-substituted diols, in which the diols are transformed into dioxolanes of the 2,2′-bridged biphenyl ketone. Efficient transfer of chirality from the diol to the twisted biphenyl occurs and then the absolute configuration of the diols can be determined simply by recognising the prevailing sense of twist of the biphenyl moiety. The relationship between the sense and angle of torsion of a biphenyl moiety and its CD spectrum is clearly and reliably established. The method in the cited reference is reported for commercially available (*R*,*R*)-pentane-2,4-diol, as an example of an *anti*-1,3-diol and the CD spectrum shows the same curve of adduct **10** as reported in Fig. 2.

The absolute configuration of the analogous *syn* compounds **8** and **9** have been determined by comparison of the optical rotation of known compound (−)-**8**, already reported in the literature ($[\alpha]_D = -9.0$, $c = 1.0$ in $CHCl_3$).[14]

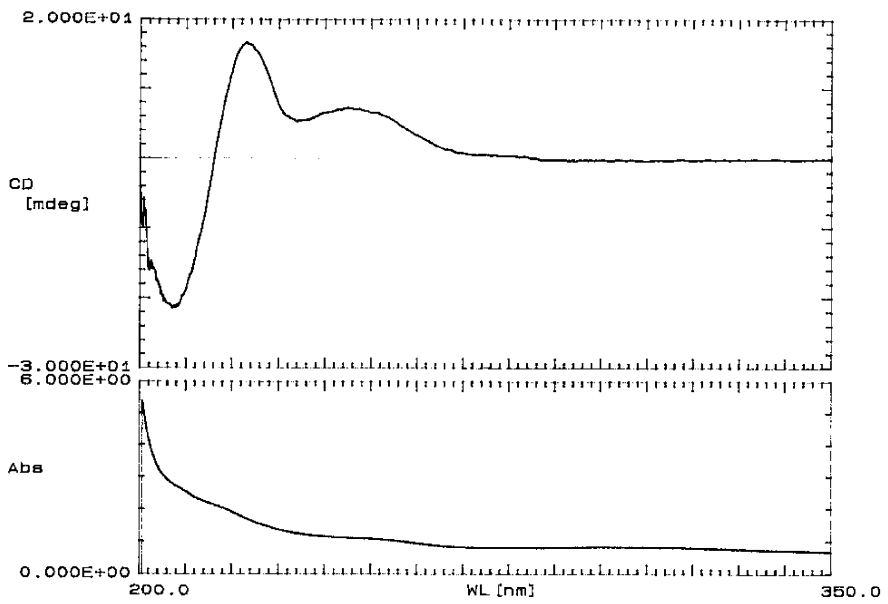
3. Conclusion

By appropriate choice of the biocatalytic reaction conditions (time and conversion rate), the present protocol allows the preparation of pairs of *anti*- and *syn*-tetrol derivatives,[15] which are useful as chiral synthons for the asymmetric synthesis of complex polyols. Studies toward this aim are under intensive investigation and the results will be reported in due course.

4. Experimental

4.1. General

All reactions were carried out in oven-dried or flame-dried glassware under nitrogen atmosphere, unless otherwise noted. All solvents were reagent grade. *n*-Hexane and propan-2-ol were all HPLC-grade and purchased from Aldrich. Acetonitrile (CH_3CN) and chloroform ($CHCl_3$) were freshly distilled from phosphoric anhydride (P_2O_5), acetic acid was freshly distilled from acetic anhydride, diethyl ether and tetrahydrofuran (THF)



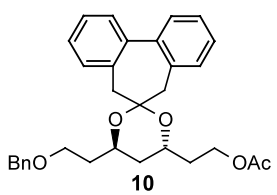


Figure 2.

were freshly distilled from sodium/benzophenone under nitrogen before use. *Pseudomonas* sp. lipase was purchased from AMANO. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75.5 MHz, respectively on a Bruker 300 spectrometer; chemical shifts being expressed in ppm with reference to $CHCl_3$, coupling constants (J) in Hz. Mass spectra were obtained on a Hewlett–Packard GC–MS 6890-5973. The optical rotations were determined with a Jasco Mod Dip-370 in $CHCl_3$. A high performance liquid chromatograph (HPLC) Hewlett–Packard 1060, equipped with a Varian 2550 absorbance detector, at 254 nm, and with a Chiralcel OJ column, was used. TLC were carried out on Merck Kieselgel precoated on silica gel 60 F-254. Column chromatographies were performed by Merck 70–230 mesh silica gel. Absorption and CD spectra were recorded on a Jasco J600 spectropolarimeter at rt in THF ($c \sim 2\times10^{-3}$ M) in 0.1 mm cell.

4.2. Methyl 7-benzyloxy-*anti*-3,5-dihydroxy-heptanoate (±)-4

A solution of tetramethylammonium triacetoxyborohydride (4.5 g, 17.14 mmol) in anhydrous CH_3CN (9.5 mL) was treated with anhydrous acetic acid (9.5 mL) and the mixture was stirred at room temperature for 0.5 h. The mixture was cooled to −40°C, and a solution of **3** (0.6 g, 2.14 mmol) in anhydrous CH_3CN (3.15 mL) was added via cannula. The mixture was stirred at −40°C for 18 h. The reaction was quenched with aqueous sodium potassium tartrate (0.5 M, 4 mL) and the mixture was allowed to warm slowly to room temperature. The mixture was diluted with dichloromethane and washed with aqueous saturated sodium bicarbonate. The aqueous layer was back-extracted with dichloromethane four times, and the combined organic layers were washed with saturated aqueous sodium bicarbonate. The aqueous layer was back-extracted four times with dichloromethane, and the combined organic layers were dried with anhydrous sodium sulphate and concentrated in vacuum.

The mixture was passed through silica gel column with petroleum ether/ethyl acetate 6:4 as eluent to give diol (±)-**4** as a colourless oil (0.434 g, 72%): R_f 0.44 (petroleum ether/ethyl acetate 6:4); ^{1}H NMR ($CDCl_3$): δ 7.36–7.20 (m, 5H), 4.5 (s, 2H), 4.40–4.28 (m, 1H), 4.18–4.08 (m, 1H); 3.74–3.52 (m, 2H), 3.68 (s, 3H), 2.60–2.42 (m, 2H), 1.98–1.54 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 171.5, 138.0, 128.0, 127.8, 73.3, 69.1, 65.8, 65.6, 51.6, 41.4, 37.9, 35.8.

4.3. Methyl 7-benzyloxy-*anti*-3,5-dihydroxy-3,5-*O*-isopropylidene-heptanoate (±)-5

Compound (±)-**4** (0.536 g, 1.9 mmol) was transformed to the acetonide (±)-**5** by standard procedure (in 2,2-dimethoxypropane (12 mL) in the presence of catalytic 10-camphorsulfonic acid) which was quenched with few drops of triethylamine and concentrated in vacuum. Silica gel chromatography (petroleum ether/ethyl acetate 7:3) gave the desired compound as a colourless oil in quantitative yield: R_f 0.85 (petroleum ether/ethyl acetate 7:3); ^{1}H NMR ($CDCl_3$): δ 7.48–7.29 (m, 5H), 4.52 (s, 2H), 4.36–4.20 (m, 1H), 4.12–3.92 (m, 1H), 3.72 (s, 3H), 3.64–3.50 (m, 2H), 2.62–2.40 (m, 2H), 1.90–1.54 (m, 4H), 1.38 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 173.0, 138.5, 128.4, 127.7, 100.6, 73.1, 69.2, 66.5, 63.5, 51.6, 40.6, 37.9, 35.9, 24.6.

4.4. 7-Benzyloxy-*anti*-3,5-*O*-isopropylidene-heptane-1,3,5-triol (±)-6

To a stirred solution of (±)-**5** (0.380 g, 1.14 mmol) in dry THF (50 mL), lithium aluminium hydride 95% ($LiAlH_4$, 0.105 g, 2.62 mmol) was slowly added at 0°C. After 0.5 h the mixture was quenched with methanol, diluted with aqueous saturated ammonium chloride, extracted with ethyl acetate and dried on anhydrous sodium sulphate to afford, after solvent evaporation, compound (±)-**6** as a pale yellow oil, in quantitative yield (0.335 g, 1.14 mmol): R_f 0.38 (petroleum ether/ethyl acetate 75:25); ^{1}H NMR ($CDCl_3$): δ 7.38–7.3 (m, 5H), 4.50 (s, 2H), 4.18–3.88 (m, 2H), 3.84–3.72 (m, 2H), 3.62–3.52 (m, 2H), 2.52 (bs, 1H), 1.88–1.7 (m, 4H), 1.7–1.6 (m, 2H), 1.38 (s, 3H), 1.32 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 138.5, 128.3, 127.6, 127.5, 100.4, 73.1, 66.8, 66.5, 63.7, 61.1, 38.2, 37.7, 35.9, 24.8, 24.7; m/z: M^+−Me, 279; (100) 91.

4.5. 1-Acetoxy-7-benzyloxy-*anti*-3,5-dihydroxy-3,5-*O*-isopropylidene-heptane (±)-7

Compound (±)-**6** (0.084 g, 0.29 mmol) was acetylated by the standard procedure (1.5 mL of triethylamine, 0.073 g (0.7 mmol) of acetic anhydride and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine). After 1 h, the mixture was quenched with methanol in an ice bath. The solvent was evaporated in vacuum and *n*-hexane was added in order to remove traces of acetic acid. The crude mixture was chromatographed on silica gel (petroleum ether/ethyl acetate 7:3) to give (±)-**7**, as a pale yellow oil in 90% yield (0.087 g, 0.25 mmol): R_f 0.87 (petroleum ether/ethyl acetate 7:3); ^{1}H NMR ($CDCl_3$): δ 7.40–7.30 (m, 5H), 4.50 (s, 2H), 4.20–4.10 (bt, 2H), 4.08–3.88 (m, 2H), 3.60–3.50 (m, 2H), 2.05 (s, 3H), 1.80–1.77 (m, 2H), 1.65–1.55 (m, 4H), 1.31 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 171.0, 138.5, 128.4, 127.9, 127.7, 100.4, 73.1, 66.6, 63.7, 63.5, 61.2, 38.5, 36.0, 34.7, 24.6, 20.9; m/z: M^+−Me, 321; (100) 91.

4.6. 1-Acetoxy-7-benzyloxy-*syn*-3,5-dihydroxy-3,5-*O*-isopropylidene-heptane (±)-9

The protocol for the esterification of (±)-**8** was the same to have compound (±)-**7** with 90% yield: R_f 0.87 (petroleum ether/ethyl acetate 7:3); ^{1}H NMR ($CDCl_3$): δ 7.42–7.28 (m, 5H), 4.50 (s, 2H), 4.22–4.12 (m, 2H), 4.10–4.0 (m, 1H), 3.98–3.88 (m, 1H), 3.64–3.5 (m, 2H), 2.08 (s, 3H), 1.88–1.68 (m, 4H), 1.42 (s, 3H), 1.38 (s, 3H), 1.32–1.18 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 173.1, 138.5, 128.2, 127.5, 98.5, 72.9, 66.0, 65.9, 60.8, 36.9, 36.4, 35.3, 30.0, 20.8, 19.6; m/z: M^+−Me, 221; (100) 91.

4.7. Enzyme-catalysed transesterification: general procedure

A solution of compound **6** or **8** (0.2 mmol) in dry Et_2O (10 mL) was vigorously shaken at room temperature. Vinyl acetate (6 mmol, 0.55 mL) and PSL (6.7 mg, 200 U) were then added in the flask and the reaction was monitored by TLC and by HPLC (*n*-hexane/propan-2-ol 95:5 v/v%, flow 0.5 mL/min). After the suitable reaction time, the suspension was filtered and washed with ethyl acetate. The organic solvent was removed in vacuum and the crude mixture was chromatographed (silica gel, eluent petroleum ether/ethyl acetate 75:25) to afford the alcohols and the acetylated compounds as reported in Table 1.

4.8. Enzyme-catalysed hydrolysis: general procedure

To compound **7** or **9** (0.15 mmol) suspended in a 0.5 M phosphate buffer solution (pH 7, 15 mL), PSL (5 mg, 150 U), was added. The reaction was monitored by TLC and by HPLC (*n*-hexane/propan-2-ol 95:5 v/v%, flow 0.5 mL/min). After the suitable reaction time the mixture was extracted many times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and evaporated to afford a crude mixture which was purified by chromatography (eluent petroleum ether/ethyl acetate 75:25) to afford the alcohols and the acetylated compounds as reported in Table 1.

4.9. Determination of enantiomeric excess of compounds 6, 7 and 8 by HPLC

The column used was Chiralcel OJ column.

For compound (±)-**6** eluent: *n*-hexane/propan-2-ol 96:4 v/v%, flow: 0.4 mL/min, retention time: $t_{(+)}=30.53$ min, $t_{(-)}=36.35$ min.

For compound (±)-**7** eluent: *n*-hexane/propan-2-ol 95:5 v/v%, flow: 0.5 mL/min, retention time: $t_{(-)}=7.54$ min, $t_{(+)}=11.38$ min.

For compound (±)-**8** eluent: *n*-hexane/propan-2-ol 95:5 v/v%, flow: 0.5 mL/min, retention time: $t_{(-)}=20.87$ min, $t_{(+)}=23.05$ min.

4.10. Determination of enantiomeric excess of compound 9 by NMR analysis

The e.e.s for the two enantiomers of compound **9** were determined by ^{1}H NMR analysis. In the presence of the chiral shift reagent, tri[3-(heptafluoropropylhydroxymethylene)-(+)camphorato] europium, $Eu(hfc)_3$, in a 0.3–0.6 molar ratio, the acetyl signal have shown a significant difference in their chemical shift values. For (+)-**9** $\delta=2.58$ ppm; for (−)-**9** $\delta=2.38$ ppm.

4.11. (3*R*,5*R*)-1-Acetoxy-7-benzyloxy-3,5-dihydroxy-3,5-*O*-[(2,2′-biphenyl)-1,3-isopropylidene]-heptane 10

To a solution of compound (+)-**7** (0.06 mmol, 20 mg) in dry THF (1 mL) was added a solution of HCl (1 M, 1 mL). After stirring the mixture for 20 min the mixture was quenched with saturated aqueous sodium bicarbonate and extracted a few times with ethyl acetate. The organic layers were dried on anhydrous sodium sulphate and the crude diol (18 mg) was immediately used to prepare the dioxolane **10**. To the above crude diol and actived 4 Å molecular sieves in dry $CHCl_3$ (4 mL) was added the dimethyl-acetal[16] of the corresponding 2,2′-bridged diphenyl ketone (16 mg) and a catalytic amount of *p*-toluensulphonic acid, at room temperature. After 2 h the reaction mixture was filtered to remove molecular sieves and the solvent was evaporated in vacuum. The crude product was then chromatographed (silica gel, petroleum ether/diethyl ether 9:1) to afford **10** as a pale yellow oil (4.5 mg, 15%). R_f: 0.5 (petroleum ether/diethyl ether 9:1); ^{1}H NMR ($CDCl_3$): δ 7.5–7.1 (m, 13H), 4.6 (bs, 2H), 4.35–4.1 (m, 4H), 3.78–3.66 (m 1H), 3.6–3.5 (m, 1H), 3.05–2.9 (m, 2H), 2.58–2.4 (m, 2H), 2.12 (s, 3H), 1.98–1.68 (m, 6H).

Acknowledgements

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