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Desymmetrisation of a Centrosymmetric Molecule by Carbon–Carbon Bond Formation: Asymmetric Aldol Reactions of a Centrosymmetric Dialdehyde

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Abstract: The desymmetrisation of centrosymmetric molecules by enantioselective carbon–carbon bond formation has been reported for the first time. A bimetallic zinc catalyst developed by Trost was exploited in the desymmetrisation of a centrosymmetric dialdehyde. The approach was successful with a range of ketone nucleophiles and was uniformly highly diastereoselective (>98:<2). The yield and the enantioselectivity of the reaction varied as a function of the ketone used, and the desymmetrised products were obtained in up to 74% yield and 97% *ee* (*ee* = enantiomeric excess). The desymmetrisation of centrosymmetric molecules by enantioselective carbon–carbon bond formation is an efficient and convergent synthetic approach which is likely to find wide application in synthesis, particularly in the total synthesis of natural products with embedded centrosymmetric fragments.

Keywords: aldol reaction · asymmetric synthesis · desymmetrisation · stereochemistry

Introduction

Desymmetrisation is a powerful strategy for asymmetric synthesis, as it can allow the preparation of highly enantiomerically enriched products in high yield.[1] Most usually, the strategy involves the desymmetrisation of a *meso* substrate with an internal mirror plane by differentiation between its enantiotopic groups with a chiral catalyst or reagent.[1] The approach can, however, be extended to substrates with other improper elements of symmetry, such as a centre of symmetry (S_2) or an S_4 symmetry operation.[2] For example, centrosymmetric molecules have been previously desymmetrised by enantioselective reduction,[3,4] acylation,[5] ester hydrolysis[6] and epoxide hydrolysis.[7] Furthermore, resistance to the S_4-symmetric antibiotic, nonactin, is conferred by its enantioselective enzymatic hydrolysis.[8]

We have previously exploited the centrosymmetric nature of key natural-product fragments in natural-product synthesis. For example, we used a two-directional[9] synthetic approach to prepare a centrosymmetric diepoxide which was subsequently desymmetrised by enantioselective epoxide hydrolysis; after acetonisation, a key intermediate in a total synthesis of hemibrevetoxin B was obtained in 98% yield and with >98% *ee*.[7] More recently, we exploited the enantioselective formylation of a centrosymmetric piperazine in a total synthesis of dragmacidin A.[5]

The power of the desymmetrisation approach may be extended through the exploitation of enantioselective connective reactions which increase synthetic convergency. For example, a range of carbon–carbon bond-forming reactions have been used in the desymmetrisation of *meso* dialdehydes with an internal mirror plane: enantioselective Horner–Wadsworth–Emmons reactions,[10] organozinc additions,[11] allylations[12] and aldol reactions.[13] An auxiliary-controlled diastereoselective aldol reaction was exploited in a total synthesis of denitculatin A.[13a] Here, we report the first desymmetrisation of a centrosymmetric molecule by an enantioselective carbon–carbon bond-forming reaction. In addition to the requirement for efficient enantiotopic group differentiation, the approach additionally raises the issue of diastereoselectivity. This type of transformation may find application in the synthesis of natural products with hidden centrosymmetric fragments.

Results and Discussion

The centrosymmetric dialdehyde **1** was prepared by using a modified version of our reported synthetic route.[7] The desymmetrisation reaction was investigated by using a direct

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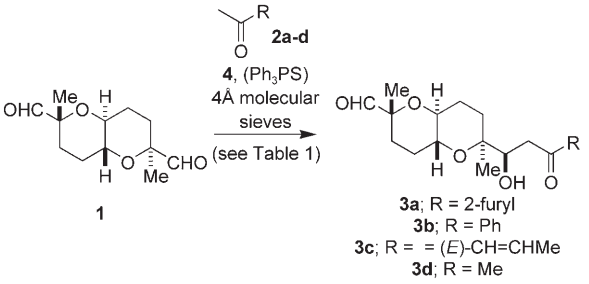
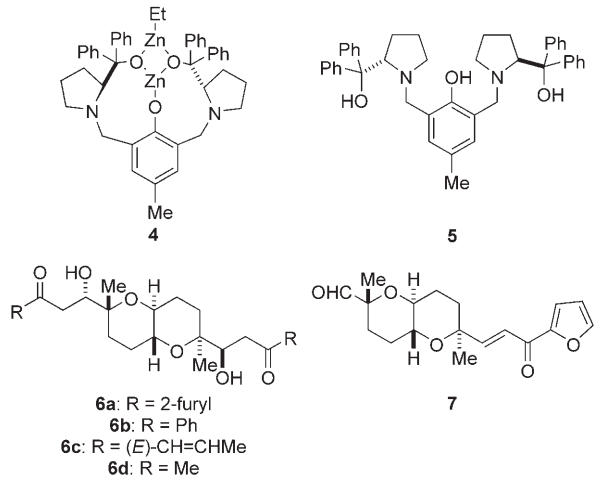
asymmetric aldol reaction involving a bimetallic zinc catalyst, **4**, which has been developed in Trost's laboratory (Scheme 1).[14] The enantioselectivity of the reaction was



Scheme 1. Desymmetrisation of a centrosymmetric dialdehyde by direct enantioselective aldol reaction.



measured by chiral analytical HPLC by comparison with the appropriate racemic standards (see the Supporting Information). Our results are summarised in Table 1.

The active catalyst, **4**,[14b] formed in situ by treatment of the chiral ligand **5** (one equivalent) with a solution of diethylzinc in hexane (two equivalents), was investigated in the desymmetrisation of the centrosymmetric diadehyde **1**. With a stoichoimetric amount of the catalyst and twelve equivalents of 2-acetyl furan (**2a**), the desymmetrised product **3a** was obtained with $>98:<2$ diastereoselectivity in 25% yield and with 97% *ee* after 48 hours at 5°C (entry 1a, Table 1). Here, the low yield of the required desymmetrised product **3a** stemmed from two side reactions, addition of a second equivalent of the nucleophile to yield the centrosymmetric product **6a** and β-elimination to give the enone **7**. The relative configuration of the product **2a** was determined by X-ray crystallography (Figure 1). As with the addition of other nucleophiles to the dialdehyde **1**,[7] the relative stereochemical outcome of the reaction was consistent with

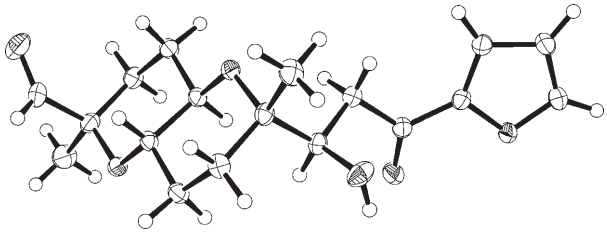


Figure 1. X-ray crystal structure of the desymmetrised compound **3a**.

Felkin–Anh-controlled[15,16] addition to the less-hindered diastereotopic face of the axial formyl group (Figure 2).

We have assigned the absolute configuration of the product **3a** by using two reactions with a highly reliable stereochemical outcome (Scheme 2).[17–19] We demonstrated that the Corey–Bakshi–Shibata (CBS) reduction[17,18] of ketone **8**, prepared by silylation of the aldol **3a**, was reagent controlled: reduction by using the enantiomeric catalysts (*R*)- and

Table 1. Desymmetrisation of the centrosymmetric dialdehyde **1** by direct asymmetric aldol reaction.

Entry	Ketone (equiv)[a]	R	*c* [M][b]	Cat. **4** [mol%][a]	Ph_3PS[a] [mol%]	*t* [h]	*T* [°C]	Solvent	Yield **3** [%][c]	*ee* **3** [%][d]	Yield **6** [%][c]
1a	**2a** (12)	2-furyl	0.6	100	0	48	5	THF	25	97	13[e]
1b	**2a** (12)	2-furyl	0.6	100	0	24	5	THF	74	97	2[e]
1c	**2a** (12)	2-furyl	0.6	100	15	18	5	THF	73	97	20[e]
1d	**2a** (12)	2-furyl	0.6	20	15	24	5	THF	47	94	0
1e	**2a** (12)	2-furyl	0.6	20	15	48	5	THF	38	>98	0
1f	**2a** (12)	2-furyl	1.2	20	15	48	5	THF	36	96	0
1g	**2a** (12)	2-furyl	0.6	20	15	48	25	THF	70	74	0
1h	**2a** (12)	2-furyl	0.6	20	15	48	5	CH_2Cl_2	33	86	0
1i	**2a** (12)	2-furyl	0.6	20	15	48	5	Et_2O	36	56	0
2a	**2b** (10)	Ph	0.6	100	15	24	5	THF	41	91	42
2b	**2b** (5)	Ph	0.6	100	15	20	5	THF	42	95	7
2c	**2b** (5)	Ph	0.6	100	15	4.5	5	THF	57	98	0
3a	**2c** (10)	(*E*)-CH=CHMe	0.6	100	15	20	5	THF	40	57	15
3b	**2c** (10)	(*E*)-CH=CHMe	0.6	100	15	4	5	THF	48	53	19
4a	**2d** (10)	Me	0.6	100	15	4	5	THF	31	66	14
4b	**2d** (10)	Me	0.6	100	15	20	5	THF	36	84	15

[a] Relative to the dialdehyde **1**. [b] Concentration of dialdehyde **1**. [c] Yield of purified product. [d] Determined by chiral analytical HPLC. [e] Analysis of the crude reaction mixture by 500 MHz ^{1}H NMR spectroscopy revealed that **6a** and **7** were both present.

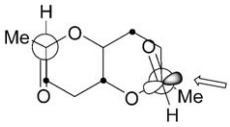
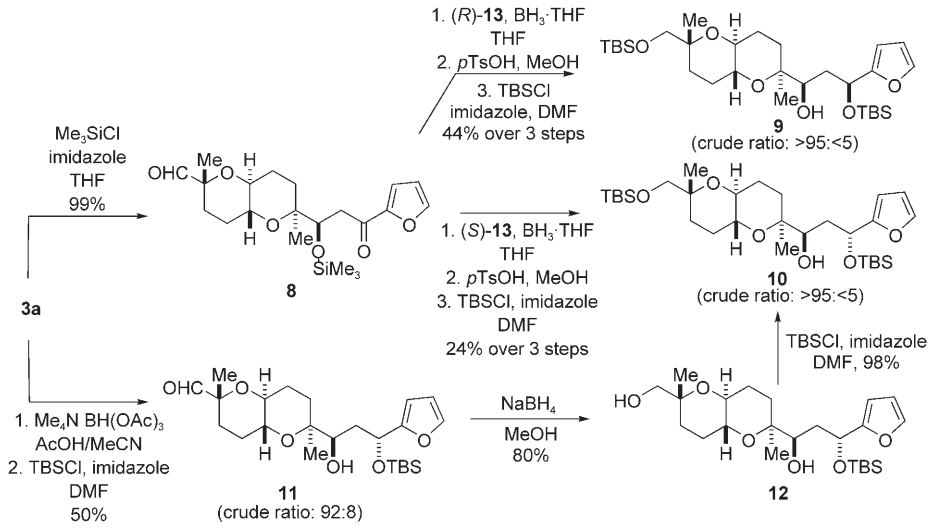
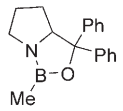


Figure 2. Model to explain the diastereoselectivity of the desymmetrisation reaction.



Scheme 2. Determination of the absolute configuration of the desymmetrised product **3a**.

(*S*)-**13**, followed by desilylation and di-*tert*-butyldimethylsilylation, gave the diastereoisomeric products **9** and **10**, respectively, each with $>95:<5$ diastereoselectivity. Directed reduction of the aldol **3a** with tetramethylammonium triacetoxyborohydride[19] gave the corresponding 1,3-*anti* diol without reduction of the formyl group; *tert*-butyldimethylsilylation gave the aldehyde **11**. Reduction of the aldehyde **11** and *tert*-butyldimethylsilylation gave the bis-silyl ether **10**, which was spectroscopically identical to that obtained previously. The stereochemical outcome of the desymmetrisation **1**→**3a** is consistent with the highly *re*-selective addition of ketone enolates to a wide range of aldehydes observed under the control of the catalyst **4**.[14] The desymmetrisation **1**→**3a** is, thus, controlled by the addition of the ketone enolate to the aldehyde face for which substrate control (Felkin–Anh control) and reagent control (addition to the *re* face with catalyst **4**) are matched.



13

Optimisation of the reaction time suppressed the second aldol reaction and after 24 h, the required desymmetrised product **3a** was obtained in 74% yield with 97% *ee* (entry 1b). The reaction time could be shortened by the introduction of 15 mol% Ph_3PS: under these conditions, the desymmetrised product **3a** was obtained in 73% yield and with 97% *ee* after 18 h (entry 1c). Ph_3PS has been previously noted to act as a weak coordinating agent for zinc, and to improve turnover by displacing the aldol product from the catalyst.[14b]

With an effective desymmetrisation reaction in hand, we turned our attention to the use of sub-stoichiometric (20 mol%) quantities of the chiral catalyst (entries 1d–i). Under these conditions, the reaction was rather sluggish. With 15 mol% Ph_3PS and 20 mol% of the catalyst **4**, the desymmetrised product **3a** was obtained in 47% yield with 94% *ee* after 24 h, along with 47% of the recovered centrosymmetric dialdehyde. A range of parameters (reaction time, concentration, temperature and solvent) were varied in an attempt to optimise the reaction with 20 mol% of the catalyst. Increasing the reaction time (entry 1e) or the concentration (entry 1f) did not increase the yield of the required product. Furthermore, although increasing the reaction temperature to 25°C did give an improved 70% yield of the product, its enantiomeric excess (74%) had been seriously eroded (entry 1g). Changing of reaction solvent to either dichloromethane or diethyl ether did not improve the yield of the product and had an unfavourable effect on the enantioselectivity of the reaction (compare entries 1h and 1i with entry 1d).

We extended our investigation to a range of other ketone nucleophiles (**2b–d**) (entries 2–4). As the desymmetrisation of the centrosymmetric dialdehyde **1** with 2-acetyl furan as the nucleophile had been most effective with 100 mol% of **4**, we focussed on investigating the scope of the desymmetrisation process under similar, stoichiometric conditions. Unfortunately, the conditions which had been optimal for 2-acetyl furan (**2a**) were not ideal with other nucleophiles, and further optimisation was required for each ketone. However, in each case, the desymmetrised product (**3b–d**) was obtained with $>98:<2$ diastereoselectivity.

For example, with acetophenone (**2b**), extended reaction times (20 h) gave only 35% yield of the desymmetrised product due to significant addition of a second equivalent of ketone to the required product (→**6b**) (entry 2a, Table 1). However, the use of 100 mol% of **4** and five equivalents of ketone yielded the desymmetrised product **3b** in 57% yield and with 98% *ee* after 4.5 hours at 5°C (entry 2b). A shorter reaction time was also required in the optimisation of the reaction with (*E*)-pent-4-en-2-one (compare entries 3a and 3b) and the required desymmetrised product **3c** was obtained in 48% yield after four hours at 5°C, although the enantiomeric excess (53% *ee*) observed was rather low in this case (entry 3b). In the case of acetone, a longer reaction time was required and the desymmetrised product **3d** was

obtained in 36% yield and with 84% *ee* after 20 hours at 5°C (entry 4b). Here, the variation of the enantiomeric excess of the product with increased reaction time suggested that kinetic resolution of the desymmetrised product and, hence, enhancement of its albeit moderate enantiomeric excess was occurring with increased conversion (compare entries 4a and 4b).[20]

Conclusion

We have demonstrated for the first time that the desymmetrisation of centrosymmetric molecules by enantioselective carbon–carbon bond formation can be an efficient and convergent synthetic approach. In particular, by using Trost's bimetallic zinc catalyst **4**, desymmetrisation of the centrosymmetric dialdehyde **1** was effective with a range of ketone nucleophiles and excellent enantiotopic formyl-group differentiation was possible in some cases. The desymmetrisation of centrosymmetric molecules by enantioselective carbon–carbon bond formation is likely to find wide application in synthesis, particularly in the total synthesis of natural products with embedded centrosymmetric fragments.[2] In addition, through elaboration of the furyl ketone **3a**,[21] the approach may find application in the total synthesis of the marine natural product hemibrevetoxin B.

Experimental Section

General procedure for the desymmetrisation of the dialdehyde 1: A solution of diethylzinc (700 μL of a 1.0 M in hexanes, 0.7 mmol) was added to a solution of the ligand **5** (224 mg, 0.35 mmol) under an argon atmosphere in THF (3.5 mL) at room temperature and stirred for 0.5 h. A solution of the catalyst (3.54 mL of an approximately 0.1 M solution in THF, 0.354 mmol) was then added to a suspension of dialdehyde **1** (80 mg, 0.354 mmol), powdered 4 Å molecular sieves (87 mg), triphenylphosphine sulfide (15.6 mg, 15 mol%, 53 μmol) and a ketone (**2a–d**, either 1.77 or 3.54 mmol) in THF (563 μL) at 0°C. The reaction mixture was stirred for 4–18 h at 5°C and then aqueous hydrochloric acid solution (1 M, 5 mL) was added and the organic layer was separated. The aqueous layer was extracted with diethyl ether (3×10 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to give a crude product.

(3*R*,8a′*S*,2′*R*,4a′*R*,6′*S*) 1-Furan-2-yl-3-hydroxy-3-(6′-hydroxymethyl-2′,6′-dimethyloctahydropyrano[3′,2′-*b*]pyran-2′-yl)propan-1-one (3a): A solution of diethylzinc (400 μL of a 1.0 M in hexanes, 0.4 mmol) was added to a solution of ligand **5** (128 mg, 0.20 mmol) under an argon atmosphere in THF (2.0 mL) at room temperature and stirred for 0.5 h. A solution of catalyst **4** (1.86 mL of an approximately 0.1 M solution in THF, 0.186 mmol) was then added to a suspension of dialdehyde **1** (42 mg, 0.186 mmol), powdered 4 Å molecular sieves (37.2 mg), triphenylphosphine sulfide (8.2 mg, 15 mol%, 28 μmol) and acetyl furan (206 μL, 2.23 mmol) in THF (295 μL) at 0°C. The reaction mixture was stirred for 24 h at 5°C and then aqueous hydrochloric acid solution (1 M, 5 mL) was added and the organic layer was separated. The aqueous layer was washed with ether (3×10 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to afford the crude product. Purification by flash column chromatography (silica gel, EtOAc/petroleum ether (b.p. 40–60°C) 4:6) gave the desymmetrised product **3a** (46.0 mg, 74%) as colourless needles. M.p. 161.5–164.2°C (from EtOAc); $[\alpha]_D = -13.2$ ($c = 1$ in $CHCl_3$); $R_f = 0.34$ (EtOAc/petroleum ether (b.p. 40–60°C) 4:6); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): $\delta = 9.61$ (1H, d, $J =$ 1.7 Hz; C*H*O), 7.62 (1H, dd, $J = 1.7$, 0.6 Hz; Fu 5-H), 7.24 (1H, dd, $J =$ 3.6, 0.6 Hz; Fu 3-H), 6.57 (1H, dd, $J = 3.4$, 1.7 Hz; Fu 4-H), 4.79 (1H, dd, $J = 10$, 1.5 Hz; 3-H), 3.22 (1H, dd, $J = 17.5$, 1.7 Hz; 2-H_A), 3.15 (1H, dt, $J = 9.4$, 4.1 Hz; 1′-H or 5′-H), 3.11 (1H, dt, $J = 9.4$, 4.3 Hz; 1′-H or 5′-H), 2.93 (1H, dd, $J = 17.7$, 10.3 Hz; 2-H_B), 2.34 (1H, dt, $J = 14.1$, 3.4 Hz; 7′-H_{eq}), 2.25 (1H, ddd, $J = 14.1$, 4.3, 2.8 Hz; 3′-H_{eq}), 1.94–1.88 (1H, m; 8′-H_{eq}), 1.81–1.68 (2H, m; 4′-H_{eq}, 3′-H_{ax}), 1.51–1.42 (2H, m; 8′-H_{ax}, 7′-H_{ax}), 1.34–1.24 (4′-H_{ax}), 1.15 (3H, s; 2-Me), 1.14 ppm (3H, s; 6-Me); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C, TMS): $\delta = 205.4$ (CHO), 190.4 (1-C), 152.8 (Fu 2-C), 147.1 (Fu 5-C), 118.2 (Fu 3-C), 112.7 (Fu 4-C), 80.9 (2′-C), 76.3 (1′-C), 75.3 (6′-C), 70.8 (5′-C), 65.0 (3-C), 39.1 (2-C), 31.7 (7′-C), 30.2 (3′-C), 27.8 (4′-C), 25.9 (8′-C), 23.4 (Me), 22.7 (Me); IR (film): $\tilde{\nu} = 3521$ (m), 3140–2700 (br), 1735 (s), 1660 cm^{-1} (s); ESMS: m/z: 337.2 (35) $[M]^+$, 319.2 (100) $[M-OH]^+$; HRMS: m/z: calcd for $C_{18}H_{24}O_6$: 337.1662 $[M+H]^+$; found: 337.1662; elemental analysis calcd (%) for $C_{18}H_{24}O_6$: C 64.3, H 7.20; found: C 64.3, H 7.20.

Analysis by chiral analytical HPLC (OD Chiralcel; UV detection at $\lambda =$ 280 nm; 90:10 hexane-IPA) revealed that the sample had a value of 97% *ee*.

Also obtained, by further flash column chromatography (silica gel, EtOAc/petrol (2:8)) was the centrosymmetric product **6a** (6.0 mg, 0.014 mmol, 13%).

(3*R*,8a′*S*,2′*R*,4a′*R*,6′*S*) 6′-(1-Hydroxy-3-oxo-3-phenylpropyl)-2′,6′-dimethyloctahydropyrano[3,2-*b*]pyran-2′-carbaldehyde (3b): A solution of diethylzinc (1.6 mL of a 1.0 M solution in hexanes, 1.6 mmol) was added to a solution of ligand **5** (512 mg, 0.80 mmol) under an argon atmosphere in THF (8.0 mL) at room temperature. The mixture was then stirred for 0.5 h. After this time, a solution of catalyst **4** (3.54 mL of an approximately 0.1 M solution in THF, 0.354 mmol) was added to a suspension of dialdehyde **1** (80 mg, 0.354 mmol), powdered 4 Å molecular sieves (87.0 mg), triphenylphosphine sulfide (15.6 mg, 15 mol%, 56 μmol) and acetophenone (207 μL, 1.76 mmol) in THF (563 μL) at 0°C. The reaction mixture was stirred for 4.5 h at 5°C and then aqueous hydrochloric acid solution (1 M, 5 mL) was added and the organic layer was separated. The aqueous layer was washed with diethyl ether (3×10 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated in vacuo to afford the crude product. Purification by flash column chromatography (silica gel, EtOAc/petrol 4:6) gave the desymmetrised product **3b** (68 mg, 57%) as a colourless powder. M.p. 143.2–147.8°C (EtOAc); $[\alpha]_D = -6.4$ ($c = 1$ in $CHCl_3$); $R_f = 0.59$ (4:6 EtOAc/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$, 25°C, TMS): $\delta = 9.61$ (1H, app s; C*H*O), 8.00 (2H, d, $J = 8.0$ Hz; Ar 6-H, Ar 2-H), 7.63–7.58 (1H, m; Ar-4H), 7.50 (2H, app t, $J = 7.7$ Hz; Ar 3-H, Ar 5-H), 4.83 (1H, dd, $J = 9.4$, 3.2 Hz; 1-H), 3.36 (1H, app d, $J = 18$ Hz; 2-H_A), 3.15–3.10 (2H, m; 1′-H, 5′-H), 3.06 (1H, dd, $J = 18.4$, 10.3 Hz; 2-H_B), 2.38 (1H, dt, $J = 14.1$, 3.4 Hz; 7′-H_{eq}), 2.24 (1H, dt, $J = 13.7$, 3.4 Hz; 3′-H_{eq}), 1.95–1.87 (1H, m; 8′-H_{eq}), 1.86–1.74 (1H, m; 4′-H_{eq}), 1.74–1.67 (1H, m; 3′-H_{ax}), 1.52–1.41 (2H, m; 7′-H_{ax}, 8′-H_{ax}), 1.36–1.24 (1H, m; 4′-H_{ax}), 1.18 (3H, s; Me), 1.15 ppm (3H, s; Me); ^{13}C NMR (125 MHz, $CDCl_3$, 25°C, TMS): $\delta = 205.0$ (CHO), 201.5 (1-C), 136.7 (Ar), 133.6 (Ar), 128.7 (Ar), 128.1 (Ar), 80.5 (2′-C), 76.0 (1′-C), 75.1 (6-C), 70.5 (5′-C), 65.4 (3-C), 38.8 (2-C), 31.4 (7′-C), 31.4 (3′-C), 27.4 (4′-C), 25.6 (C8′), 23.0 (Me), 22.5 (Me); IR (film): $\tilde{\nu} = 3522$ (m), 3056–2700 (br), 1739 (s), 1676 (s), 1448 cm^{-1} (m); ESMS: m/z: 346.8 (100) $[M]^+$, 328.8 (49) $[M-OH]^+$; HRMS: m/z: calcd for $C_{20}H_{26}O_5$: 369.1678 $[M+Na]^+$; found: 369.1693.

Analysis by chiral analytical HPLC (OD Chiralcel; UV detection at $\lambda =$ 225 nm; gradient elution: 95:5→5:95 hexane/IPA) revealed that the sample had 98% *ee*.

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