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Asymmetric synthesis of (−)-bissetone via a highly enantioselective hetero-Diels–Alder reaction

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ABSTRACT

We demonstrate a new approach for the asymmetric synthesis of bissetone. The key reaction is the highly enantioselective hetero-Diels–Alder cycloaddition of triene **3** with ethyl glyoxylate catalyzed by readily available BINOL–Ti complexes. The HDA cycloadduct **4** was then transformed in five steps into O-protected bissetone (**8**) and its C5-epimer in good yield.

1. Introduction

Bissetone is one of the naturally occurring metabolites of 1,5-anhydro-D-fructose having an antimicrobial activity, and is isolated from the very polar extracts of the Gorgonian soft coral *Briareum polyanthes*.[1] 1,5-Anhydro-D-fructose is produced with the help of α-1,4-glucan lyase by the degradation of glycogen, starch or maltosaccharides. This compound and its derivatives and metabolites like bissetone, haliclonol, palythazine, isopalythazine, 1-deoxymannojirimycin, 5-epipentenomycin I, or clavulazine are very interesting molecules due to their pharmaceutical potential (Fig. 1).[2]

Bissetone is a tetrahydro-4*H*-pyran-4-one functionalized in positions 2 and 5 and containing two stereogenic centers. The structure and relative stereochemistry of bissetone were assigned by X-ray diffraction analysis.[1] The absolute configuration was confirmed by chemical synthesis from D-glucose by Lichtenthaler.[3]

Bissetone was obtained from D-glucose in eight steps in 37% overall yield (Scheme 1).[3] Firstly, D-glucose was transformed into a dihydropyranone intermediate with one stereogenic center. After addition of the lithium enolate of acetone to the carbonyl group of the dihydropyranone, the (−)-BzO-protected bissetone was obtained in 64% yield. Alternatively, methylallyl titanium triisopropoxide could be used as an acetone synthon, although required an additional ozonation step.

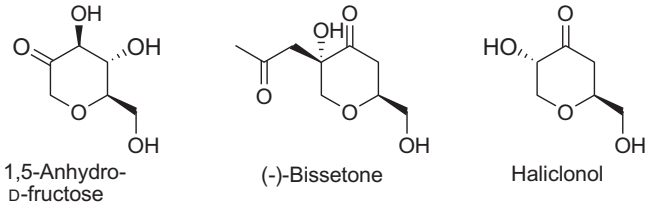

Fig. 1. '1,5-Anhydro-D-fructose and its metabolites'.

2. Results and discussion

In this paper, we demonstrate a new approach to the synthesis of bissetone and its stereoisomers. As a key step, our strategy involved the use of an enantioselective hetero-Diels–Alder reaction[4] for the construction of a six-membered oxo-ring with a stereogenic center in position 2 (Scheme 2). The second stereogenic center at C5

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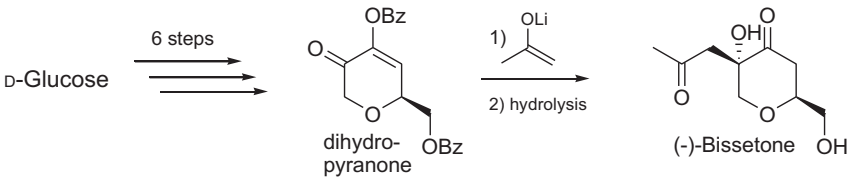
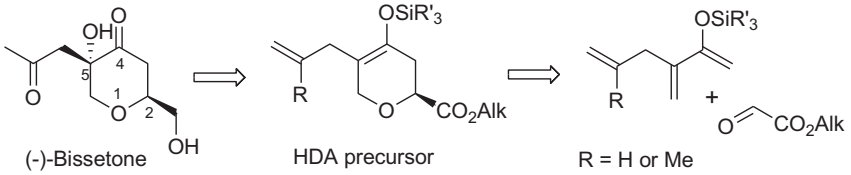


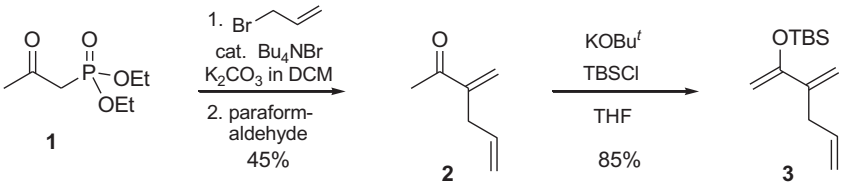
Scheme 1. The synthesis of (−)-bissetone from D-glucose by Lichtenthaler.



Scheme 2. The retrosynthetic analysis of bissetone.

with a tertiary hydroxyl group and carbonyl at C4 would be introduced via Rubottom oxidation of a silyl enol ether moiety.[5,6] Finally, our synthetic plan envisioned formation of an *exo*-cyclic carbonyl group (acetone subunit) by ozonation (R=Me) or Wacker–Tsuji oxidation (R=H)[7] of the corresponding alkene moiety and deprotection of the primary alcohol.

Initially, triene **3** for the hetero-Diels–Alder reaction was prepared (Scheme 3). Firstly, diethyl (2-oxopropyl)phosphonate (**1**)[8] was alkylated with allyl bromide in the presence of K_2CO_3 and a catalytic amount of tetrabutylammonium bromide. The subsequent Horner–Wadsworth–Emmons reaction was carried out in the same flask by addition of paraformaldehyde. The reaction yield in this step was moderate (45%) due to *gem*-diallylation of **1**. Finally, the TBS-protected triene **3** was obtained from ketone **2** and *tert*-butyldimethylsilyl chloride in the presence of 2 equiv of Bu^{t}OK in 85% yield.



Scheme 3. The synthesis of triene **3** for the HDA reaction.

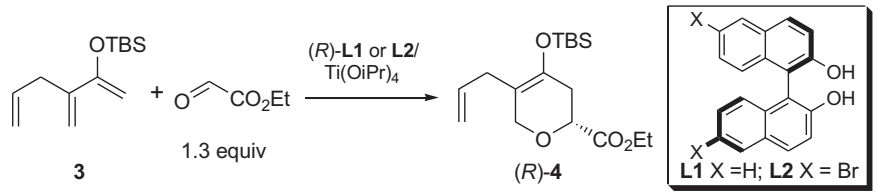
The enantioselective hetero-Diels–Alder reaction of the triene **3** and commercially available ethyl glyoxylate was used as the key step for the construction of the oxo six-membered ring framework (Table 1). The literature describes several catalytic systems useful in HDA reactions of glyoxylates with non-activated[9] as well as activated 1-alkoxy 1,3-dienes[10] and Danishefsky-type dienes.[11] Oxo-Diels–Alder reactions of 1,3-dienes with one activating group in position 2 are rare in the literature.[12] To the best of our knowledge, HDA reactions with 2-silyloxy-3-alkyl dienes of type **3** proposed in our retrosynthetic analysis have not been previously reported. Among various catalytic systems, we concentrated our attention on BINOL–titanium complexes, which have been applied successfully in asymmetric catalysis, including hetero-Diels–Alder reactions, by Mikami,[10a–c,13] and Keck.[14] Recently, we also demonstrated very efficient Friedel–Crafts type reactions of activated heteroarenes with glyoxylates in the presence of BINOL–Ti catalyst.[15]

Titanium complexes generated from binaphthol and Ti(O^{i}Pr)$_4$ using the Keck[14] method were found to be very useful asymmetric catalysts in this cycloaddition reaction (Table 1). Optimization of the reaction conditions showed that 5 mol % of [(*R*)-6,6′-dibromo-BINOL]$_2$Ti complex in toluene[16] gave the highest enantioselectivity (up to 98.5% ee, entry 8) and good yield (73%) of the product **4**. Importantly, 1 mol % of the same catalyst in a more concentrated reaction mixture (0.4 mL of toluene on a 1 mmol scale) led to comparable results (71% yield, 98% ee, entry 9). Using a catalyst with an unsubstituted binaphthol gave product **4** with slightly lower enantioselectivity (90–93% ee vs 95–98% ee, entries 1, 2, 9, and 10). The use of (*R*)-BINOL–Ti catalysts resulted in formation of the (*R*)-enantiomer of cycloadduct **4**. The observed direction of the asymmetric induction is in agreement with enantioselective HDA reactions of glyoxylates catalyzed by BINOL–Ti complexes reported in the literarure.[10a–e]

In the synthesis of natural (−)-bissetone, a titanium catalyst based on (*S*)-6,6′-dibromo-BINOL was applied in the hetero-Diels–Alder reaction. In the next step, the cycloadduct **4** was reduced with $LiAlH_4$ to the corresponding alcohol **5** in practically quantitative yield and with unchanged optical purity (Scheme 4).[17] The primary alcohol **5** was protected by either trityl or benzoyl groups (see products **6a** and **6b**). We expected that the larger protecting group (i.e., Tr) at this position could increase diastereoselectivity in the oxidation step.

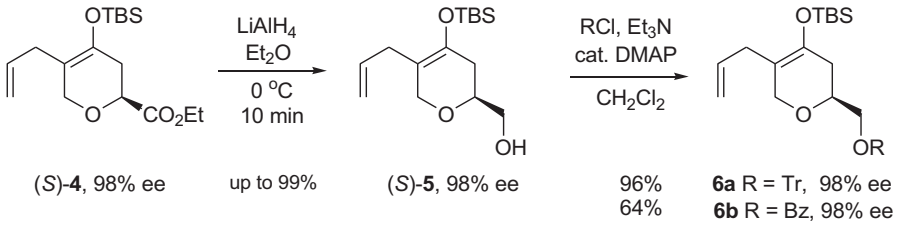
Oxidation of TBS-protected enols **6a** and **6b** containing the allyl substituent with *meta*-chloroperoxybenzoic acid (*m*-CPBA) under optimized conditions, followed by desilylation with $Bu_4NF\cdot 3H_2O$, led chemoselectively to the expected products **7a** and **7b** in good yields (70–90%), but unfortunately with practically no diastereoselectivity (~1:1 mixture of cis/trans) (Scheme 5).[6] Other commonly used oxidation conditions (OsO_4/NMO, Na_2WO_4/H_2O_2, *t*-BuOOH, Oxone/K_2CO_3/cyclohexanone) failed in this reaction. We concentrated our efforts on oxidation with *m*-CPBA in various solvents (AcOEt, toluene, CH_2Cl_2, THF, MeOH, hexane, cyclohexane, MeCN) and also with base additives (e.g., K_2CO_3, $NaHCO_3$, K_2HPO_4, Et_3N). Unfortunately, in many cases, a mixture of products difficult

Table 1
The enantioselective hetero-Diels–Alder reaction



Entry	Catalyst	mol %	Solvent[a] (mL/mmol)	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	**L1**/Ti(O^{i}Pr)$_4$ (1:1)	5%	CH_2Cl_2 (dry) (0.8)	0	4	89	90
2	**L2**/Ti(O^{i}Pr)$_4$ (1:1)	5%	CH_2Cl_2 (dry) (0.8)	0	4	90	95
3	**L2**/Ti(O^{i}Pr)$_4$ (1:1)	5%	Toluene (0.8)	0	4	83	96.5
4	**L2**/Ti(O^{i}Pr)$_4$ (1:1)	5%	Toluene (0.8)	0	2.5	52	96
5	**L2**/Ti(O^{i}Pr)$_4$ (1:1)	5%	Toluene (0.8)	20	5	73	97
6	**L2**/Ti(O^{i}Pr)$_4$ (1:1)	1%	Toluene (0.16)	0	5	45	94
7	**L2**/Ti(O^{i}Pr)$_4$ (1:1)	1%	Toluene (0.16)	0→20	20	81	95
8	**L2**/Ti(O^{i}Pr)$_4$ (2:1)	5%	Toluene (2.0)	0→20	5	73	98.5
9	**L2**/Ti(O^{i}Pr)$_4$ (2:1)	1%	Toluene (0.4)	0→20	20	71	98
10	**L1**/Ti(O^{i}Pr)$_4$ (2:1)	2%	Toluene (1.0)	0	15	80	93

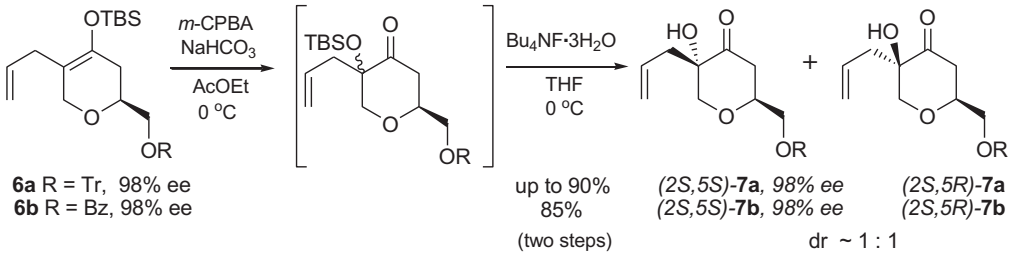
Conditions: triene **3** (1.0 mmol), ethyl glyoxylate (1.3 mmol) in toluene or CH_2Cl_2.
[a] Use of dry toluene is not necessary for high enantioselectivity.



Scheme 4.

for characterizing was observed. Finally, the best results in the terms of yield were obtained with *m*-CPBA in AcOEt and toluene. The mixture of diastereoisomers of products **7a** and **7b** could be separated by careful chromatography on silica.

trityl group was easily removed from (2*S*,5*S*)-**8a** in the presence of $FeCl_3 \cdot 6H_2O$ in dichloromethane to afford (−)-bissetone in 78% yield. Hydrolysis of **8b** under basic conditions was previously described.[3]



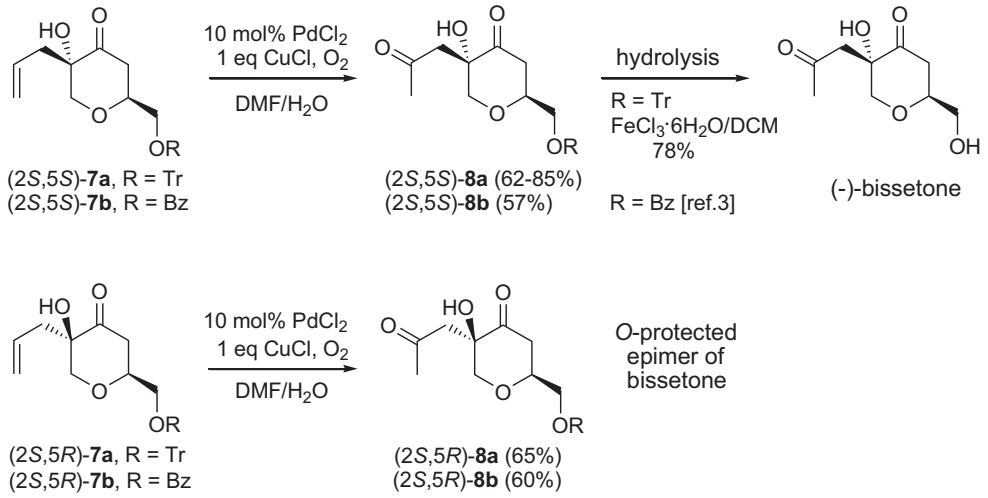
Scheme 5. Oxidation of the silyl enol ethers **6a** and **6b**.

In the next step, single diastereoisomers of **7a** and **7b** were oxidized under Wacker–Tsuji conditions (O_2, $PdCl_2$, CuCl)[7] to give O-protected bissetone ((2*S*,5*S*)-**8a**/**8b**) or the corresponding C5-epimers (2*S*,5*R*)-**8a**/**8b** with 57–85% yield (Scheme 6). Optionally, mixtures of diastereoisomers **7** could be oxidized and separated.

The structure of diastereoisomers **8a** was assigned by NMR experiments and X-ray analysis of *trans*-**8a** (Fig. 2). The structure and absolute configuration of (2*S*,5*S*)-**8b** were confirmed by comparison to the literature data (NMR and optical rotation).[3] The

3. Conclusions

A simple and efficient enantioselective approach to bissetone and its stereoisomers has been proposed. O-Protected bissetone **8** and its 5-epimer were obtained in good overall yield (up to 65% for R=Tr) in six steps starting from a hetero-Diels–Alder reaction. A highly enantioselective HDA cycloaddition of 2,3-substituted diene and glyoxylate catalyzed by easily available BINOL–Ti was demonstrated. Despite the efficiency of our approach, the most challenging step is still the control of diastereoselectivity in the



Scheme 6. The Wacker–Tsuji oxidation.

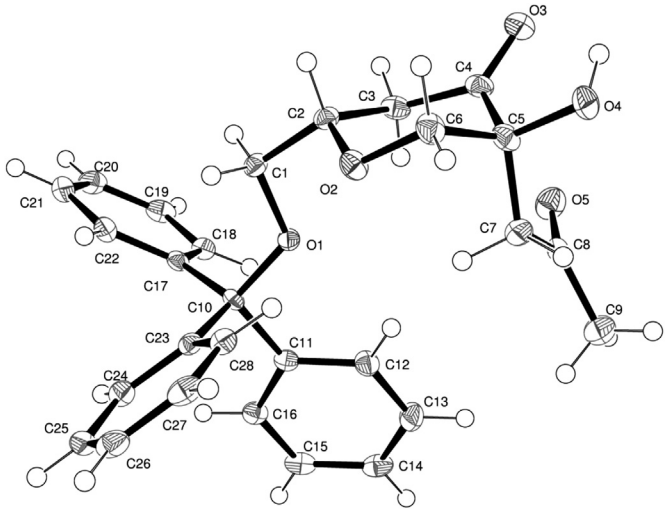


Fig. 2. X-ray crystal structure of (±)-TrO-protected bissetone (*trans*-**8a**).

oxidation of silyl enol ether, and this issue requires more attention in the future. Finally, stereoisomer (2*S*,5*S*)-**7a** was oxidized under Wacker–Tsuji conditions and deprotected to afford the (−)-bissetone.

4. Experimental section

4.1. General information

All reported NMR spectra were recorded on a Varian 400, 500 or 600 using $CDCl_3$ as solvent and $(CH_3)_4Si$ as internal standard. Chemical shifts of ^1H NMR and ^{13}C NMR are reported as δ values relative to $(CH_3)_4Si$ (δ=0.00) and to the central $CDCl_3$ (δ=77.0), respectively. Coupling constants (J) in the ^1H NMR are in hertz. The following abbreviations are used to indicate the multiplicity: s—singlet; d—doublet; t—triplet; q—quartet; m—multiplet; dm—doublet of multiplets. High-resolution mass spectra (HRMS) were recorded on a Mariner PE Biosystems unit using the ESI technique. IR spectra were taken on an FT-IR Perkin–Elmer Spectrum 2000 using a film (CH_2Cl_2). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Analytical TLC was carried out on commercial plates coated with 0.25 mm of Merck Kieselgel 60. Preparative flash silica chromatography was performed using Merck Kieselgel 60 (230–400 mesh).

The enantiomeric excess (ee) of the products was determined by high performance liquid chromatography (HPLC). HPLC analyses were performed on a chromatograph fitted with the diode-array detector (DAD) and Chiralpak AD-H (250×4.6 mm, 5 μm), AS-H (250×4.6 mm, 5 μm), or Chiracel OD-H (250×4.6 mm, 5 μm) columns eluted with *iso*-propanol (1–20%) in hexane.

All solvents and commercially available chemicals were used without additional purification, unless otherwise noted. Ethyl glyoxylate was distilled under vacuum over P_2O_5 before use. (*R*)- and (*S*)-1,1′-bi-2-naphthol, ethyl glyoxylate (50% solution in toluene), and $Ti(O^iPr)_4$ (97% purity) were purchased from Aldrich. (*R*)- and (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol (**L2**) were prepared according to the procedures described in the literature.[18]

4.2. Experimental procedures and characterization data

*4.2.1. 3-Methylenehex-5-en-2-one (**2**).* A 150-mL round-bottomed flask with a stir bar was charged with (2-oxopropyl)phosphonate (10.0 g, 51 mmol)[8] in CH_2Cl_2 (40 mL), K_2CO_3 (28.5 g, 4 equiv), and 5 mol % of tetrabutylammonium bromide (0.83 g). After stirring for 0.5 h at room temperature, allyl bromide (6.9 g, 1.1 equiv) was added in one portion and reaction was continued for 2 days at room temperature in the dark. After this time, paraformaldehyde (1.89 g, 1.2 equiv) was added and reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and poured into water (200 mL). The volatile product was extracted with CH_2Cl_2 (3×20 mL), the combined organic layers were dried over $MgSO_4$, and carefully evaporated in vacuo (20 °C water bath). Vacuum distillation at 70–75 °C/80 mmHg with effective cooling (ca. −5 °C) afforded the title compound (2.64 g, 45%) as a colorless oil. IR (film) 3080, 2925, 1680, 1430, 1365, 1262, 1025, 918 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.07 (s, 1H), 5.88–5.77 (m, 2H), 5.09–5.03 (m, 2H), 3.02 (dm, J=6.7 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2 (C), 147.4 (C), 135.4 (CH), 125.7(CH_2), 116.7 (CH_2), 34.6 (CH_2), 25.8 (CH_3).

*4.2.2. 2-tert-Butyldimethylsilyloxy-3-methylenehexa-1,5-diene (**3**).* To stirred suspension of potassium *tert*-butoxide (1.02 g, 9.0 mmol) in dry THF (20 mL) cooled to −78 °C under argon atmosphere, was added dropwise 3-methylidenehex-5-en-2-one (**2**) (0.50 g, 4.5 mmol). After 10 min *tert*-butyldimethylchlorosilane (1.64 g, 10 mmol) in toluene (50% solution) was introduced and stirred for 30 min at −78 °C. The reaction mixture was warmed to −30 °C and quenched by the addition of 15% aqueous NH_4Cl (10 mL). The product was extracted with Et_2O (3×10 mL), the combined organic layers were dried over $MgSO_4$, evaporated in vacuo,

and purified by chromatography (or distillation after scale-up) to afford 856 mg of triene **3** as a colorless oil with 85% yield. IR (film) 2957, 2930, 2859, 1589, 1472, 1255, 1159, 1018, 909, 839, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96–5.80 (m, 1H), 5.56–5.52 (m, 1H), 5.14–4.99 (m, 3H), 4.54–4.50 (m, 1H), 4.36–4.33 (m, 1H), 3.00–2.95 (m, 2H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 (C), 142.7 (C), 136.5 (CH), 116.0 (CH_2), 113.8 (CH_2), 92.9 (CH_2), 37.2 (CH_2), 25.8 (3× CH_3), 18.3 (C), −4.7 (2× CH_3).

*4.2.3. (−)-(2S)-Ethyl 5-allyl-4-tert-butyldimethylsilyloxy-3,6-dihydro-2H-pyran-2-carboxylate (**4**).* A 5-mL round-bottomed flask was charged with (*S*)-6,6′-Br_2BINOL (**L2**) (45.0 mg, 0.10 mmol), toluene (2.0 mL, 0.05 M) and capped with a septum. To the stirred solution of the ligand, titanium tetraisopropoxide (14.7 μL, 14.2 mg, 0.050 mmol, 5.0 mol %) was added via syringe directly under the solution surface at room temperature (inert atmosphere is not required). The resulting dark red mixture was stirred for 2 h at room temperature and cooled to 0 °C. Ethyl glyoxylate (0.133 g, 1.3 mmol; distilled under vacuum over P_2O_5 before use) was introduced and, finally, after 5 min, 2-*tert*-butyldimethylsilyloxy-3-methylenehexa-1,5-diene (**3**) (225 mg, 1.0 mmol) was added at 0 °C. The reaction mixture was allowed to warm slowly to 20 °C and after stirring for 5 h was directly subjected to flash chromatography using hexane/AcOEt (9:1) as an eluent. Purification afforded 240 mg (73% yield) of cycloadduct **4** as a colorless oil with 98.5% ee (for other reaction conditions, see Table 1). $[\alpha]_D^{20}$ −153.2 (*c* 2.0, $CHCl_3$); IR (film) 3408, 2956, 2931, 2858, 1738, 1692, 1472, 1305, 1256, 1220, 1184, 1118, 1030, 903, 840, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.79–5.59 (m, 1H), 5.10–4.90 (m, 2H), 4.37–4.18 (m, 4H), 4.11 (d, *J*=14.8 Hz, 1H), 2.83 (dd, *J*=15.4, 6.5 Hz, 1H), 2.72 (dd, *J*=15.4, 6.5 Hz, 1H), 2.51–2.25 (m, 2H), 1.31 (t, *J*=7.1 Hz, 3H), 0.95 (sm, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9 (C=O), 139.9 (C), 135.3 (CH), 115.6 (CH_2), 111.3 (C), 73.3 (CH), 66.9 (CH_2), 61.2 (CH_2), 32.5 (CH_2), 30.4 (CH_2), 25.7 (CH_3), 18.1 (C), 14.2 (CH_3), −3.6 (CH_3), −4.90 (CH_3); HRMS calcd for $C_{17}H_{30}O_4NaSi$ [$(M+Na)^+$]: 349.1806; found: 349.1797; HPLC (Chiralpak AS-H, 1% *i*-PrOH in hexane, 1.0 mL/min, λ=206 nm, $t_{R(S)\text{-}\mathbf{4}}$=4.3 min—major, $t_{R(R)\text{-}\mathbf{4}}$=6.1 min—minor).

*4.2.4. (2S)-(5-Allyl-4-tert-butyldimethylsilyloxy-3,6-dihydro-2H-pyran-2-yl)methanol (**5**).* To a vigorously stirred solution of the cycloadduct **4** (1.00 g, 3.06 mmol) in dry Et_2O (20 mL) cooled to 0 °C, a suspension of $LiAlH_4$ (0.223 g, 6.12 mmol) in Et_2O (20 mL) was added dropwise. After 10 min, the reaction mixture was quenched by the addition of acetone (5 mL). Longer reduction time increases amount of impurities. After a few minutes, a saturated aqueous solution of Na_2SO_4 (5 mL), solid Na_2SO_4 (0.5 g), and AcOEt (20 mL) were added. The mixture was vigorously stirred to give a transparent organic phase and a gray solid phase, which was extracted with EtOAc (2×20 mL). Combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure, to give quantitatively crude primary alcohol **5** (0.87 g) as a colorless oil. IR (film) 3591, 2931, 2859, 1691, 1377, 1206, 1179, 1063, 997, 867, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76–5.63 (m, 1H), 5.06–4.93 (m, 2H), 4.09 (d, *J*=0.7 Hz, 2H), 3.73–3.64 (m, 2H), 3.62–3.53 (m, 1H), 2.86 (dd, *J*=15.1, 6.3 Hz, 1H), 2.70 (dd, *J*=15.0, 6.8 Hz, 1H), 2.25–2.11 (m, 2H), 1.91–1.81 (m, 1H), 0.93 (s, 9H), 0.13 (2×s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.7 (C), 135.6 (CH), 115.5 (CH_2), 111.4 (C), 75.1 (CH), 67.2 (CH_2), 65.4 (CH_2), 31.6 (CH_2), 30.6 (CH_2), 25.7 (CH_3), 18.1 (C), −3.6 (CH_3), −3.9 (CH_3); HRMS calcd for $C_{15}H_{28}O_3NaSi$ [$(M+Na)^+$]: 307.1700; found: 307.1699.

*4.2.5. (2S)-5-Allyl-4-tert-butyldimethylsilyloxy-2-trityloxymethyl-3,6-dihydro-2H-pyran (**6a**).* To a solution of crude alcohol **5** (0.87 g, ~3.06 mmol) in CH_2Cl_2 (15 mL), at room temperature were added Et_3N (0.62 g, 6.12 mmol), triphenylmethyl chloride (0.94 g, 3.36 mmol), and 4-dimethylaminopyridine (18 mg, 0.15 mmol). The reaction mixture was stirred under argon atmosphere for 24 h, and washed with an aqueous solution of $NaHCO_3$ (5%, 20 mL). After extraction with CH_2Cl_2 (3×10 mL), combined organic phases were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by short column chromatography using hexane/AcOEt (98:2) as an eluent. The (2*S*)-5-allyl-4-*tert*-butyldimethylsilyloxy-2-trityloxymethyl-3,6-dihydro-2*H*-pyran was isolated with 96% yield (1.54 g) and 98% ee. IR (film) 2931, 2859, 1692, 1491, 1449, 1208, 1179, 1072, 840, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.40 (m, 6H), 7.34–7.26 (m, 6H), 7.26–7.13 (m, 3H), 5.76–5.63 (m, 1H), 5.06–4.92 (m, 2H), 4.08 (s, 2H), 3.84–3.74 (m, 1H), 3.28 (dd, *J*=9.5, 5.9 Hz, 1H), 3.06 (dd, *J*=9.5, 5.2 Hz, 1H), 2.83 (dd, *J*=15.1, 5.8 Hz, 1H), 2.72 (dd, *J*=15.1, 6.8 Hz, 1H), 2.22–1.96 (m, 2H), 0.94 (s, 9H), 0.13 (2×s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0 (C), 141.0 (C), 135.8 (CH), 128.7 (CH), 127.8 (CH), 126.9 (CH), 115.3 (CH_2), 111.4 (C), 86.4 (C), 74.1 (CH), 67.3 (CH_2), 66.4 (CH_2), 33.3 (CH_2), 30.6 (CH_2), 25.7 (CH_3), 18.1 (C), −3.5 (CH_3), −3.9 (CH_3); HRMS calcd for $C_{34}H_{42}O_3NaSi$ [$(M+Na)^+$]: 549.2795; found: 549.2804; HPLC: (Chiralpak AD-H, 2% *i*-PrOH in hexane, 1.0 mL/min, λ=206 nm, t_R=3.9 min—maj or, t_R=4.3 min—minor).

*4.2.6. (2S)-(5-Allyl-4-tert-butyldimethylsilyloxy-3,6-dihydro-2H-pyran-2-yl)methyl benzoate (**6b**).* To a cooled (0 °C) solution of crude alcohol **5** (1.00 g, ~3.5 mmol), Et_3N (0.71 g, 7.0 mmol), and 4-dimethylaminopyridine (0.042 g, 0.35 mmol) in CH_2Cl_2 (20 mL), was added dropwise benzoyl chloride (0.74 g, 5.27 mmol). The reaction mixture was allowed to warm slowly to room temperature and after stirring for 1 day was washed with an aqueous solution of $NaHCO_3$ (5%, 30 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by short column chromatography using hexane/AcOEt (90:10) as an eluent. The (2*S*)-(5-allyl-4-*tert*-butyldimethylsilyloxy-3,6-dihydro-2*H*-pyran-2-yl)methyl benzoate was isolated with 63% yield (858 mg). IR (film) 2932, 2859, 1719, 1692, 1451, 1379, 1211, 1177, 1111, 876, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10–8.04 (m, 2H), 7.59–7.52 (m, 1H), 7.48–7.41 (m, 2H), 5.77–5.64 (m, 1H), 5.10–4.94 (m, 2H), 4.40 (dd, *J*=11.7, 3.9 Hz, 1H), 4.36 (dd, *J*=11.7, 6.5 Hz, 1H), 4.12 (s, 2H), 4.03–3.92 (m, 1H), 2.85 (dd, *J*=15.1, 5.8 Hz, 1H), 2.75 (dd, *J*=15.0, 6.7 Hz, 1H), 2.34–2.22 (m, 1H), 2.10–1.99 (m, 1H), 0.95 (s, 9H), 0.13 (2×s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.5 (C), 140.3 (C), 135.5 (CH), 133.0 (CH), 130.0 (C), 129.7 (CH), 128.3 (CH), 115.5 (CH_2), 111.5 (C), 72.7 (CH), 67.3 (CH_2), 66.7 (CH_2), 32.3 (CH_2), 30.6 (CH_2), 25.7 (CH_3), 18.1 (C), −3.6 (CH_3), −3.8 (CH_3); HRMS calcd for $C_{22}H_{32}O_4NaSi$ [$(M+Na)^+$]: 411.1962; found: 411.1961.

*4.2.7. Rubottom oxidation of **6a**.* To a suspension of silyl enol ether **6a** (350 mg, 0.664 mmol) and solid $NaHCO_3$ (111 mg, 1.32 mmol) in AcOEt (8 mL) at 0 °C was added dropwise a pre-cooled (0 °C) solution of *m*-CPBA (250 mg, 0.87 mmol, 60% of purity) in AcOEt (8 mL). After stirring for 1 h at 0 °C, the excess of *m*-CPBA was decomposed by addition of a saturated aqueous solution of Na_2SO_3 (1 mL). The reaction mixture was washed with an aqueous solution of $NaHCO_3$ (5%, 20 mL) and extracted with AcOEt (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in THF (10 mL), cooled to 0 °C and solution of pre-cooled (0 °C) $Bu_4NF\cdot 3H_2O$ (0.314 g, 0.99 mmol) in THF (10 mL) was added. After stirring for 15 min, an aqueous solution of $NaHCO_3$ (5%, 20 mL) was added and product was extracted with AcOEt (3×15 mL). Combined organic phases were dried over Na_2SO_4, filtered, concentrated in vacuo, and subjected to column chromatography using hexane/AcOEt (9:1) as an eluent. Purification afforded ~55:45 mixture of isomers

trans/*cis*-**7a** with 85% yield after two steps (131 mg of the first-eluted *trans*-**7a** and 111 mg of second-eluted *cis*-**7a**).

*4.2.7.1. (2S,5S)-5-Allyl-5-hydroxy-2-(trityloxymethyl)-tetrahydropyran-4-one (trans-**7a**).* $[\alpha]_D^{20}$ −60.1 (*c* 1.17, $CHCl_3$); IR (film) 3495, 2926, 2875, 1717, 1491, 1449, 1220, 1146, 1079, 1054, 926 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.37 (m, 5H), 7.36–7.18 (m, 10H), 5.84–5.69 (m, 1H), 5.19–5.10 (m, 2H), 4.21–4.12 (m, 1H), 3.84 (d, *J*=11.8 Hz, 1H), 3.70 (d, *J*=11.8 Hz, 1H), 3.44 (s, 1H), 3.29–3.19 (m, 2H), 2.76–2.61 (m, 3H), 2.43 (dd, *J*=14.3, 7.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.7 (C), 143.4 (C), 131.5 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 119.4 (CH_2), 87.2 (C), 76.7 (C), 76.3 (CH), 73.0 (CH_2), 64.9 (CH_2), 40.7 (CH_2), 39.2 (CH_2); HRMS calcd for $C_{28}H_{28}O_4Na$ [$(M+Na)^+$]: 451.1880; found: 451.1902; HPLC: 98.0% ee (Chiralpak AD-H, 3% *i*-PrOH in hexane, 1.0 mL/min, λ=206 nm, t_R=7.9 min—major, t_R=12.5 min—minor).

*4.2.7.2. (2S,5R)-5-Allyl-5-hydroxy-2-(trityloxymethyl)-tetrahydropyran-4-one (cis-**7a**).* Isomer with lower R_f value in 7:3 hexane/AcOEt compared to *trans*-**7a**; $[\alpha]_D^{20}$ +14.1 (*c* 1.24, $CHCl_3$); IR (film) 3549, 2925, 2877, 1721, 1491, 1449, 1223, 1150, 1078, 999, 925 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.43 (m, 5H), 7.38–7.11 (m, 10H), 5.78–5.66 (m, 1H), 5.22–5.09 (m, 2H), 4.09 (d, *J*=11.2 Hz, 1H), 3.83 (s, 1H), 3.80–3.72 (m, 1H), 3.32 (dd, *J*=10.6, 3.6 Hz, 2H), 3.22 (dd, *J*=9.9, 4.5 Hz, 1H), 2.88–2.70 (m, 2H), 2.58 (dd, *J*=14.3, 6.6 Hz, 1H), 2.47 (dd, *J*=14.1, 2.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.6 (C), 143.7 (C), 131.0 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 119.2 (CH_2), 86.7 (C), 78.7 (CH), 78.1 (C), 75.4 (CH_2), 65.6 (CH_2), 42.1 (CH_2), 41.1 (CH_2); HRMS calcd for $C_{28}H_{28}O_4Na$ [$(M+Na)^+$]: 451.1880; found: 451.1899; HPLC: 98.0% ee (Chiralpak AD-H, 3% *i*-PrOH in hexane, 1.0 mL/min, λ=206 nm, t_R=21.6 min—major, t_R=24.3 min—minor).

*4.2.8. Rubottom oxidation of **6b**.* To a suspension of silyl enol ether **6b** (370 mg, 0.952 mmol) and solid $NaHCO_3$ (160 mg, 1.90 mmol) in AcOEt (10 mL) at 0 °C was added dropwise a pre-cooled (0 °C) solution of *m*-CPBA (356 mg, 1.24 mmol, 60% of purity) in AcOEt (10 mL). After stirring for 1 h at 0 °C, the excess of *m*-CPBA was decomposed by addition of a saturated aqueous solution of Na_2SO_3 (1 mL). The reaction mixture was washed with an aqueous solution of $NaHCO_3$ (5%, 20 mL) and extracted with AcOEt (3×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in THF (10 mL), cooled to 0 °C and solution of pre-cooled (0 °C) $Bu_4NF\cdot 3H_2O$ (0.450 g, 1.43 mmol) in THF (10 mL) was added. After stirring for 15 min, an aqueous solution of $NaHCO_3$ (5%, 20 mL) was added and product was extracted with AcOEt (3×15 mL). Combined organic phases were dried over Na_2SO_4, filtered, concentrated in vacuo, and subjected to column chromatography using hexane/AcOEt (9:1) as an eluent. Purification afforded ~1:1 mixture of isomers *trans*/*cis*-**7b** with 90% yield after two steps (128 mg of the first-eluted *trans*-**7b** and 122 mg of second-eluted *cis*-**7b**).

*4.2.8.1. ((2S,5S)-5-Allyl-5-hydroxy-4-oxo-tetrahydro-2H-pyran-2-yl)methyl benzoate (trans-**7b**).* $[\alpha]_D^{20}$ −87.4 (*c* 1.14, $CHCl_3$); IR (film) 3497, 2959, 2863, 1721, 1452, 1177, 1148, 1111, 1044, 926 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04–7.95 (m, 2H), 7.55–7.49 (m, 1H), 7.45–7.35 (m, 2H), 5.72–5.57 (m, 1H), 5.15–5.01 (m, 2H), 4.47–4.30 (m, 2H), 4.04 (d, *J*=11.3 Hz, 1H), 4.00–3.90 (m, 1H), 3.75 (s, 1H), 3.31 (d, *J*=11.4 Hz, 1H), 2.77–2.61 (m, 2H), 2.60–2.44 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.4 (C), 166.1 (C), 133.4 (CH), 130.8 (CH), 129.7 (CH), 129.5 (C), 128.5 (CH), 119.4 (CH), 77.9 (C), 77.1 (CH), 75.2 (CH_2), 65.9 (CH_2), 41.6 (CH_2), 41.1 (CH_2); HRMS calcd for $C_{16}H_{18}O_5Na$ [$(M+Na)^+$]: 313.1047; found: 313.1054.

*4.2.8.2. ((2S,5R)-5-Allyl-5-hydroxy-4-oxo-tetrahydro-2H-pyran-2-yl)methyl benzoate (cis-**7b**).* Isomer with lower R_f value in 7:3 hexane/AcOEt compared to *trans*-**7b**; $[\alpha]_D^{20}$ +30.5 (*c* 1.20, $CHCl_3$); IR (film) 3553, 2957, 1723, 1602, 1452, 1316, 1178, 1151, 1113, 1071, 926 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.05–7.98 (m, 2H), 7.62–7.54 (m, 1H), 7.49–7.41 (m, 2H), 5.84–5.72 (m, 1H), 5.23–5.13 (m, 2H), 4.54 (dd, *J*=11.9, 6.3 Hz, 1H), 4.47–4.40 (m, 1H), 4.38 (dd, *J*=11.9, 3.6 Hz, 1H), 3.94 (d, *J*=12.0 Hz, 1H), 3.78 (d, *J*=12.0 Hz, 1H), 3.46 (s, 1H), 2.87–2.74 (m, 2H), 2.70 (dd, *J*=14.3, 7.2 Hz, 1H), 2.45 (dd, *J*=14.3, 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.0 (C), 166.1 (C), 133.3 (CH), 131.2 (CH), 129.7 (CH), 129.4 (C), 128.5 (CH), 119.7 (CH_2), 76.7 (C), 74.9 (CH), 72.9 (CH_2), 65.4 (CH_2), 40.2 (CH_2), 39.1 (CH_2); HRMS calcd for $C_{16}H_{18}O_5Na$ [$(M+Na)^+$]: 313.1047; found: 313.1050.

*4.2.9. Wacker–Tsuji oxidation: (2S,5S)-5-hydroxy-5-(2-oxopropyl)-2-(trityloxymethyl)-tetrahydropyran-4-one (trans-**8a**).* A 25-mL round-bottomed flask was charged with (2*S*,5*S*)-*trans*-**7a** (122 mg, 0.284 mmol), $PdCl_2$ (5.1 mg, 0.029 mmol), CuCl (29 mg, 0.29 mmol) in a 7:1 mixture of DMF (5 mL) and H_2O (0.72 mL). The resulting dark-brown solution was stirred at room temperature under an oxygen atmosphere (1 atm). After 12 h, an aqueous solution of $NaHCO_3$ (5%, 5 mL) was added and extracted with Et_2O (10 mL) and next with AcOEt (2×10 mL). The combined organic phases were dried over Na_2SO_4, filtered, concentrated in vacuo, and purified by column chromatography using hexane/AcOEt (8:2) as an eluent. The product *trans*-**8a** was isolated as a white solid with yield in the range of 62–85%. (2*S*,5*S*)-**8a**: $[\alpha]_D^{20}$ −20.2 (*c* 1.2, $CHCl_3$); IR (film) 3458, 3058, 2872, 1724, 1679, 1490, 1449, 1359, 1215, 1153, 1125, 1078, 747, 705 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.45–7.35 (m, 6H), 7.33–7.26 (m, 6H), 7.26–7.20 (m, 3H), 4.19 (s, 1H), 4.01 (d, *J*=11.2 Hz, 1H), 3.79–3.70 (m, 1H), 3.37 (d, *J*=16.7 Hz, 1H), 3.27 (dd, *J*=9.9, 4.3 Hz, 1H), 3.24–3.16 (m, 2H), 3.12 (d, *J*=16.7 Hz, 1H), 2.91–2.78 (m, *J*=13.3, 11.6 Hz, 1H), 2.58 (dd, *J*=13.4, 2.8 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 207.9 (C), 206.3 (C), 143.6 (C), 128.6 (CH), 127.9 (CH), 127.2 (CH), 86.8 (C), 79.6 (CH), 76.4 (CH_2), 65.6 (CH_2), 50.1 (CH_2), 42.3 (CH_2), 31.3 (CH_3); HRMS calcd for $C_{28}H_{28}O_5Na$ [$(M+Na)^+$]: 467.1829; found: 467.1852; HPLC: 98.0% ee (Chiralpak AD-H, 5% *i*-PrOH in hexane, 1.0 mL/min, λ=206 nm, t_R=18.2 min—major, t_R=22.2 min—minor).

*4.2.9.1. (2S,5R)-5-Hydroxy-5-(2-oxopropyl)-2-(trityloxymethyl)-tetrahydropyran-4-one (cis-**8a**).* Prepared according to the analogous procedure for *trans*-**8a**. The product *cis*-**8a** was isolated with 65% yield. IR (film) 3425, 3058, 2925, 1719, 1491, 1448, 1412, 1362, 1221, 1177, 1093, 1076, 765, 706 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.48–7.42 (m, 6H), 7.34–7.28 (m, 6H), 7.28–7.23 (m, 3H), 4.83 (s, 1H), 4.03 (d, *J*=12.0 Hz, 1H), 3.92–3.85 (m, 1H), 3.51 (d, *J*=12.0 Hz, 1H), 3.36 (dd, *J*=9.8, 5.5 Hz, 1H), 3.20 (dd, *J*=9.8, 5.1 Hz, 1H), 3.09–3.00 (m, 1H), 2.90 (d, *J*=16.7 Hz, 1H), 2.54–2.39 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.5 (C), 206.6 (C), 143.6 (C), 128.6 (CH), 127.9 (CH), 127.1 (CH), 86.8 (C), 78.4 (CH), 77.4 (C), 75.3 (CH_2), 65.6 (CH_2), 43.5 (CH_2), 41.7 (CH_2), 31.5 (CH_3); HPLC: 98.0% ee (Chiralpak AD-H, 5% *i*-PrOH in hexane, 1.0 mL/min, λ=206 nm, t_R=25.3 min—minor, t_R=28.5 min—major); LRMS calcd for $C_{28}H_{28}O_5Na$ [$(M+Na)^+$]: 467.2; found: 467.2.

*4.2.9.2. ((2S,5S)-5-Hydroxy-5-(2-oxopropyl)-4-oxo-tetrahydro-2H-pyran-2-yl)methyl benzoate (trans-**8b**).* Prepared according to the analogous procedure for *trans*-**8a**. The product (2*S*,5*S*)-**8b** was isolated with 57% yield. $[\alpha]_D^{20}$ −31.1 (*c* 0.9, $CHCl_3$) [lit.,[3b] $[\alpha]_D^{20}$ −31.6 (*c* 1.2, $CHCl_3$)]; IR (film) 3456, 2859, 1722, 1451, 1361, 1274, 1157, 1112, 1071, 713 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.10–8.00 (m, 2H), 7.61–7.55 (m, 1H), 7.48–7.42 (m, 2H), 4.47 (dd, *J*=11.8, 3.8 Hz, 1H), 4.42 (dd, *J*=11.8, 5.7 Hz, 1H), 4.20 (s, 1H), 4.03 (d, *J*=11.3 Hz, 1H), 4.02–3.97 (m, 1H), 3.33 (d, *J*=16.6 Hz, 1H), 3.26 (d, *J*=11.3 Hz, 1H), 3.12 (d, *J*=16.6 Hz, 1H), 2.88–2.81 (m, 1H), 2.72 (dd, *J*=13.3, 2.8 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.8 (C), 206.3 (C),

166.00 (C), 133.3 (CH), 129.6 (CH), 129.5 (C), 128.5 (CH), 78.0 (CH), 76.8 (C), 76.2 (CH_2), 65.8 (CH_2), 50.0 (CH_2), 41.8 (CH_2), 31.4 (CH_3); HRMS calcd for $C_{16}H_{18}O_6Na$ [$(M+Na)^+$]: 329.0996; found: 329.1002.

*4.2.9.3. ((2S,5R)-5-Hydroxy-5-(2-oxopropyl)-4-oxo-tetrahydro-2H-pyran-2-yl)methyl benzoate (cis-**8b**).* Prepared according to the analogous procedure for *trans*-**8a**. The product (2*S*,5*R*)-**8b** was isolated with 60% yield. IR (film) 3441, 2958, 1719, 1451, 1362, 1275, 1177, 1113, 1071, 713 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J=7.8 Hz, 2H), 7.58 (t, J=7.4 Hz, 1H), 7.45 (t, J=7.8 Hz, 2H), 4.99–4.86 (m, 1H), 4.48 (dd, J=11.8, 6.3 Hz, 1H), 4.42 (dd, J=11.8, 4.0 Hz, 1H), 4.08 (dd, J=11.2, 4.9 Hz, 2H), 3.53 (d, J=12.1 Hz, 1H), 3.17 (dd, J=13.4, 10.5 Hz, 1H), 2.90 (d, J=16.9 Hz, 1H), 2.52 (dd, J=13.4, 3.2 Hz, 1H), 2.44 (d, J=16.9 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 209.5 (C), 205.8 (C), 166.2 (C), 133.2 (CH), 129.7 (CH), 129.5 (C), 128.4 (CH), 77.4 (C), 76.8 (CH), 75.3 (CH_2), 65.9 (CH_2), 43.3 (CH_2), 40.8 (CH_2), 31.5 (CH_3); LRMS calcd for $C_{16}H_{18}O_6Na$ [$(M+Na)^+$]: 329.3; found: 329.1.

4.2.10. (−)-Bissetone. To a solution of (2*S*,5*S*)-**8a** (100 mg, 0.225 mmol) in CH_2Cl_2 (8 mL) was added solid $FeCl_3 \cdot 6H_2O$ (122 mg, 0.45 mmol). The mixture was stirred at room temperature, monitored by TLC and after 0.5 h was directly subjected to flash chromatography using hexane/AcOEt (4:1)→AcOEt as an eluent. Purification afforded 36 mg of a colorless oil (78% yield). $[\alpha]_D^{20}$ −52.1 (*c* 0.5, $CHCl_3$) [lit.,[3b] $[\alpha]_D^{20}$ −69.4 (*c* 1.0, EtOH)]; ^1H NMR (400 MHz, $CDCl_3$) δ 4.19 (br s, 1H), 4.04 (d, J=11.3 Hz, 1H), 3.80 (dd, J=11.8, 2.8 Hz, 1H), 3.74 (dm, J=11.7 Hz, 1H), 3.62 (dd, J=11.8, 5.2 Hz, 1H), 3.28 (d, J=16.5 Hz, 1H), 3.26 (d, J=11.3 Hz, 1H), 3.11 (d, J=16.5 Hz, 1H), 2.87 (dd, J=13.3, 11.6 Hz, 1H), 2.54 (dd, J=13.3, 2.7 Hz, 1H), 2.21 (s, 3H) 1.7 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6 (C=O), 206.3 (C=O), 80.6 (CH), 77.2 (C), 76.2 (CH_2), 64.9 (CH_2), 49.8 (CH_2), 41.1 (CH_2), 31.5 (CH_3); LRMS calcd for $C_9H_{14}O_5Na$ [$(M+Na)^+$]: 225.1; found: 225.0.

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Supplementary data

Copies of ^1H, ^{13}C NMR spectra, HPLC chromatograms, and crystallographic data. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.07.048.

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