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Formal Synthesis of (–)-Siccanin Using an Enantioselective Domino Wacker/Carbonylation/Methoxylation Reaction

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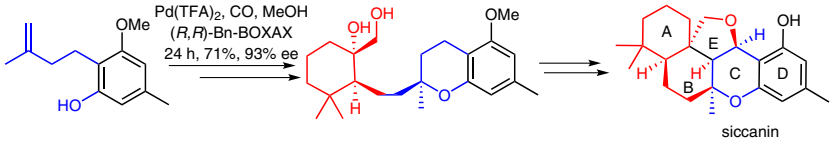

Dedicated to Professor Steven V. Ley on the occasion of his 70th birthday

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Abstract A formal synthesis of (–)-siccanin was achieved through an enantioselective domino Wacker/carbonylation/methoxylation reaction as the key step to form the chroman ring with a quaternary stereogenic center with 95% ee. The pendant cyclohexyl moiety was introduced through a two-step aldol condensation.

Key words natural products, domino reaction, aldol reaction, transition-metal catalysis, enantioselective reactions

Siccanin (**1**) and the structurally related siccanochromenes **2** and **3** are fungal metabolites that were first isolated from the culture broth of *Helminthosporium siccans* (Figure 1).[1] Siccanin (**1**) is a structurally fascinating fused pentacyclic chroman with two quaternary carbon stereogenic centers. X-ray crystallography and spectroscopic analysis unveiled the structure and absolute configuration with an unusual *cis*,*syn*,*cis*-fused A,B,C-ring system.[2]

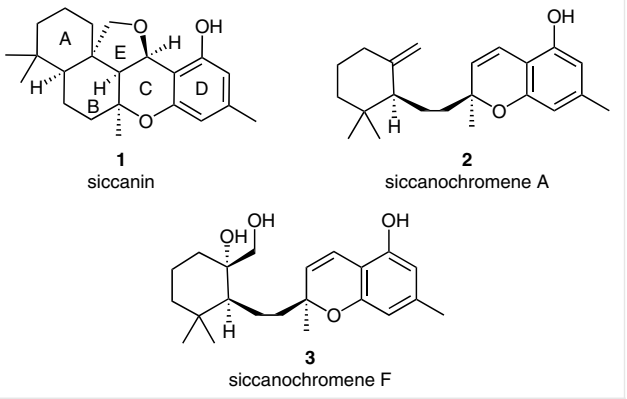


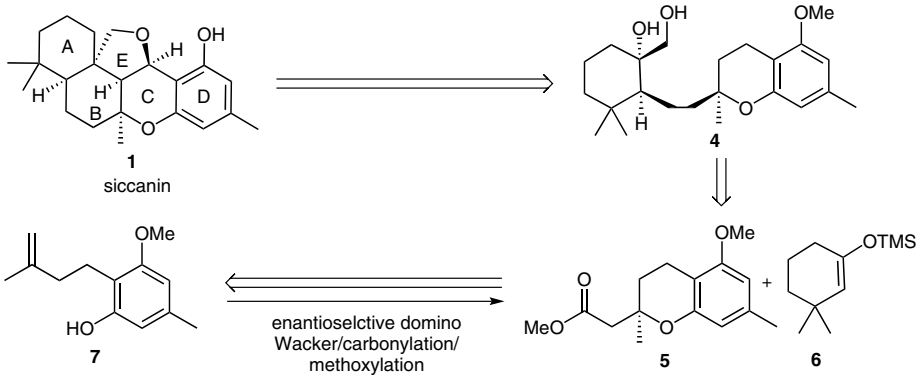
Figure 1 Siccanin (**1**) and siccanochromenes **2**–**3**

Siccanin (**1**) is a potent antifungal agent that shows strong activity against several pathogenic fungi and it has been demonstrated in clinical trials that the compound is highly effective against surface mycosis.[3] In addition, it shows significant inhibition against the growth of *Trichophyton mentagrophytes* and blocks species-selective succinate dehydrogenase.[4] The siccanochromenes (e.g., **2** and **3**) possess potent antibacterial, cytotoxic, antifungal, and insecticidal activities.[5] Several compounds of this family are regarded as intermediates in the biosynthesis of siccanin.

Despite the biological importance and structurally challenging features of siccanin (**1**), there is only one enantioselective synthesis of this compound described so far, which was developed by Trost et al.[6] They used a Pd-catalyzed asymmetric allylic alkylation and a radical epoxy olefin cyclization as key steps with diol **4** as a late intermediate.[7] Recently, Barrero et al. reported a synthesis of siccanochromene F (**3**) from (+)-3,4-dihydro-γ-ionone, isolated from *Bellardia trixago*.[8]

As part of our ongoing research towards the enantioselective domino construction of quaternary stereogenic carbon centers in natural product synthesis, we identified diol **4** as a ready target for the formal total synthesis of siccanin (**1**).[9] We envisaged that **4** would be easily accessible from silyl enol ether **6** and chiral chroman **5**, which, in turn, could be obtained from **7** by a palladium-catalyzed asymmetric domino Wacker/carbonylation/methoxylation reaction (Scheme 1).[10]

Our approach commenced with the enantioselective domino Wacker/carbonylation/methoxylation reaction of alkenyl phenol **7** in the presence of palladium (II)-trifluoroacetate (5 mol%), chiral (*R*,*R*)-Bn-BOXAX ligand **10** (20 mol%) and *p*-benzoquinone as reoxidant under an atmosphere of carbon monoxide in methanol at room temperature. The reaction afforded chiral chroman **5** in 71% yield and with 95% ee (Scheme 2).[11] Upon careful reduction of **5**



Scheme 1 Retrosynthetic analysis of Siccanin (**1**)

with diisobutylaluminum hydride (DIBAL-H) at –78 °C in toluene, aldehyde **8** was obtained in 81% yield along with 16% over-reduced alcohol **9**. However, to obtain enantiopure aldehyde **8** and working on a large scale, **5** was quantitatively reduced to give **9** by using lithium aluminum hydride in diethyl ether at room temperature. The product was then purified by preparative HPLC on a chiral phase (IA-column) allowing an increase of the ee value to 99%. Enantiopure **9** was subsequently oxidized to provide aldehyde **8** with 2-iodoxybenzoic acid (IBX) with 78% yield (Scheme 2).

The next challenging step in the synthesis was the aldol reaction of aldehyde **8** with silyl enol ether **6**, which was readily accessible on a large scale by following a reported protocol.[12] Initially, aldehyde **8** and TMS enol ether **6** were reacted with $BF_3{\cdot}OEt_2$ in CH_2Cl_2–Et_2O (9:1) at –78 °C. After full conversion of **8**, attempts were made to conduct a dehydration of the primarily formed aldol adduct **11** by acidic workup and activation of the alcohol moiety and subsequent elimination by using DEAD/PPh_3,[13] MsCl/DBU,[14] or Ac_2O/pyridine, respectively. Unfortunately, all attempts at the elimination were unsuccessful. To circumvent this problem, crude aldol adduct **11** was reacted with Burgess reagent[15] **15** (Figure 2) under microwave irradiation at 80 °C in toluene to give the desired α,β-unsaturated ketones (*E*)-**12** and (*Z*)-**13** in 8 and 20% yield, together with 13% yield of constitutional isomer (*E*)-**14** (Table 1, entry 1). To improve the yield of (*E*)-**12** and to suppress the formation of (*E*)-**14**, several other milder conditions were investigated. Reasonable results were achieved by transmetalation of the TMS enol ether **6** with methyl lithium followed by a second transmetalation with $ZnCl_2$, and subsequent addition of aldehyde **8** to the formed Zn-enolate and elimination with Martin's sulfurane[16] **16**. In this way, (*E*)-**12** and (*Z*)-**13** were obtained in 44 and 16% yield, respectively (entry 4).

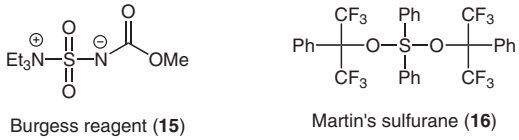
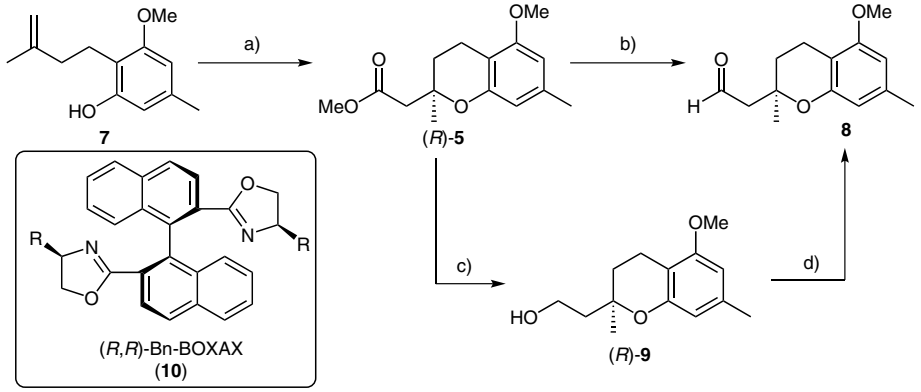
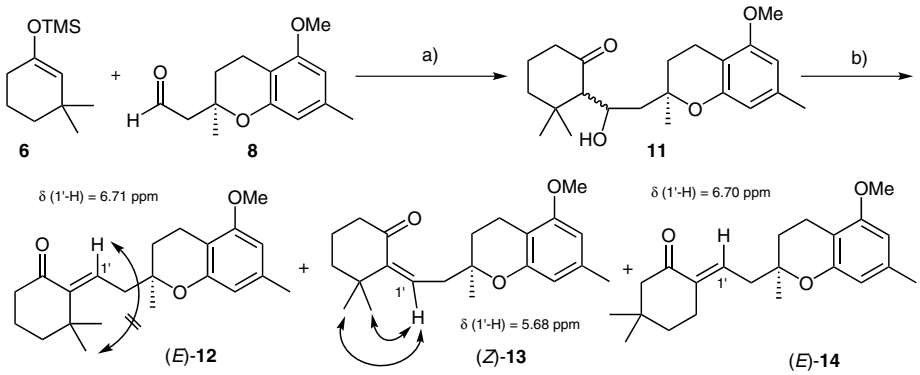


Figure 2 Structures of the reagents used herein



Scheme 2 Synthesis of aldehyde **8**: *Reagents and conditions*: (a) $Pd(TFA)_2$ (5 mol%), (*R*,*R*)-Bn-BOXAX (**10**) (20 mol%), *p*-benzoquinone (4.0 equiv), MeOH, CO (1 atm), r.t., 24 h, 71%, 93% ee; (b) DIBAL-H (2.5 equiv), toluene, –78 °C, 20 min, 81% (*R*)-**8**, 16% (*R*)-**9**; (c) $LiAlH_4$ (1.1 equiv), Et_2O, 0 °C→r.t., 3 h, quant.; (1) IBX (2.0 equiv), DMSO, r.t., 2 h, 78%.

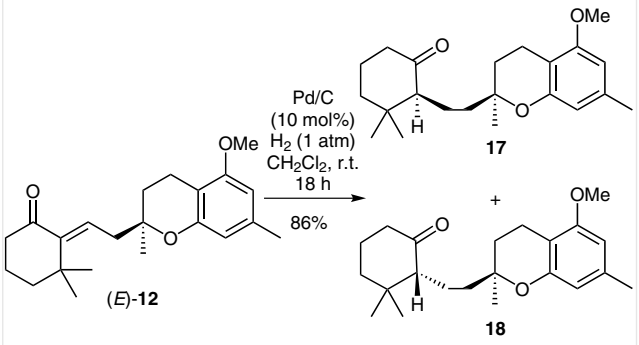
Table 1 Aldol Condensation of Aldehyde **8** and Silyl Enol Ether **6**



Entry	Conditions (a)	Conditions (b)	Yield (%)		
			(*E*)-**12**	(*Z*)-**13**	(*E*)-**14**
1	**8**, BF_3·OEt_2, **6**, CH_2Cl_2/Et_2O, –78 °C, 23 h	**15**, toluene, 80 °C, MW, 30 min	8	20	13
2	i. **6**, MeLi, THF, 0 °C, 30 min; ii. **8**, –78 °C, 4 h	**16**, CH_2Cl_2, 0 °C to r.t., 30 min	21	14	–
3	i. **6**, MeLi, Et_2O, 0 °C, 1 h; ii. $MgBr_2$·OEt_2, 0 °C, 40 min iii. **8**, –78 °C, 16 h	**16**, CH_2Cl_2, 0 °C to r.t., 3 h	47	7	–
4	i. **6**, MeLi, THF, 0 °C, 30 min; ii. $ZnCl_2$, –78 °C, 1 h; iii. **8**, –78 °C, 16 h	**16**, CH_2Cl_2, 0 °C to r.t., 2 h	44	16	–

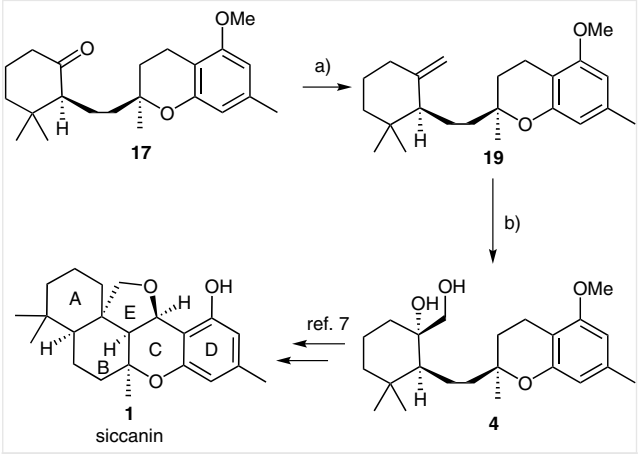
For the continuation of our synthesis, the chemoselective hydrogenation of the α,β-unsaturated ketone (*E*)-**12** was investigated. The best results were obtained by performing the reaction with palladium on charcoal (10 mol%) in CH_2Cl_2 at room temperature under a hydrogen atmosphere (1 atm) for 18 hours. A diastereomeric mixture of **17** and **18** (1:1.1 ratio) with 86% yield was obtained, which could be separated by preparative HPLC on a chiral IB column (Scheme 3). In addition, based on reported protocols, several homogeneous hydrogenation reaction conditions were carried out. Interestingly, neither hydrogenation of (*E*)-**18** using Wilkinson, Crabtree or a ruthenium catalyst with a BINAP backbone nor Noyori's transfer hydrogenation procedures were successful.

The double bond geometry of the α,β-unsaturated ketones (*E*)-**12**, (*Z*)-**13**, and (*E*)-**14** was assigned by taking the different chemical shifts of the vinyl proton 1'-H into account. The magnetic anisotropy of the carbonyl group in (*E*)-**12** and the side-product (*E*)-**14** exerts a strong deshielding effect on 1'-H, whereas the carbonyl group in isomer (*Z*)-**13** does not have such an effect. The assignments for (*E*)-**12** and (*Z*)-**13** were further supported by NOE experiments.



Scheme 3 Hydrogenation of α,β-unsaturated ketone (*E*)-**12**

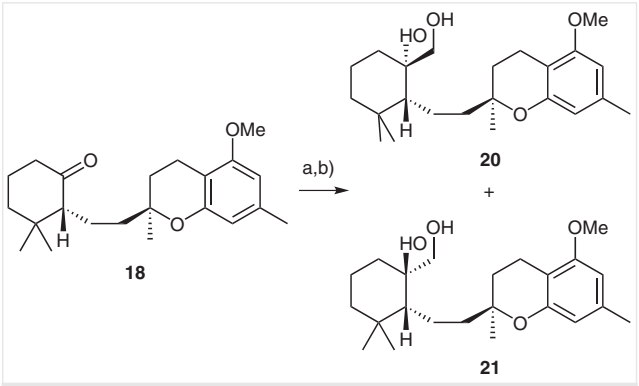
The next step in the synthesis involved the transformation of the carbonyl group into an olefin moiety. Initially, the non-basic Lombardo methylenation was applied; unfortunately, the reaction did not afford any product. Wittig reaction of **17** with the ylide of $MePPh_3Br$ and *t*-BuOK formed in situ in THF also did not give the desired compound. However, from this reaction we learned that, based on NMR analysis of the recovered starting material, the stereochemical integrity of the α-position of ketone **17** is not affected under basic conditions. Thus, when *t*-BuOK used in the Wittig reaction was replaced by the more basic *n*-BuLi under reflux conditions, the reaction afforded 38% alkene **19** and 57% recovered starting material. Finally, Peterson olefination of **17** gave the best yields. For this reaction, trimethylsilylmethyl magnesium, which was obtained from chloromethyltrimethylsilane, magnesium and LiCl, was added to ketone **17** to afford the corresponding diastereomeric alcohols in a 1:1 ratio. Subsequently, the alcohol mixture was reacted with NaH in THF at 100 °C under microwave irradiation to yield alkene **19** in 85% yield over two steps (Scheme 4). We note here that a similar problem had been encountered by us in the synthesis of desogestrel; in that case, Peterson olefination was the only way to introduce a methylene group starting from a cyclic ketone.[17]



Scheme 4 *Reagents and conditions*: (a) i. $TMSCH_2MgCl$, LiCl, Et_2O, 0 °C to r.t., 20 h; ii. NaH, THF, 100 °C, MW, 16 h; (b) AD-mix-β, $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH–H_2O (1:1), 5 d, 90%.

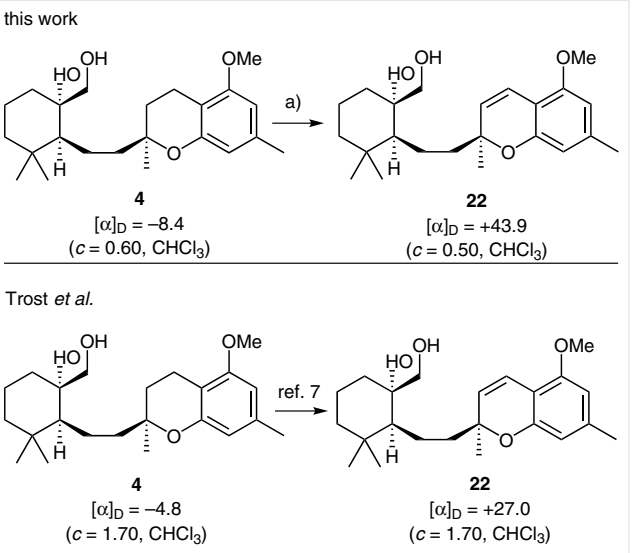
To complete the formal synthesis of siccanin (**1**), alkene **19** was subjected to Sharpless dihydroxylation with AD-mix-β in the presence of methanesulfonamide in *t*-BuOH–H_2O (1:1) at room temperature to give **4** exclusively as a single diastereomer in 90% yield (Scheme 4). As already mentioned, diol **4** is a late intermediate in the synthesis of siccanin (**1**) developed by Trost et al.[6]

We also transformed the diastereomeric ketone **18** obtained in the hydrogenation of (*E*)-**12** into diols **20** and **21** (Scheme 5) and treated diol **4** with DDQ to obtain the corresponding chromene **22** (Scheme 6).



Scheme 5 Synthesis of diols **20** and **21**. *Reagents and conditions*: (a) i. $TMSCH_2MgCl$, LiCl, Et_2O, 0 °C to r.t., 20 h; ii. NaH, THF, 100 °C, MW, 16 h; (b) AD-mix-β, $MeSO_2NH_2$ (1.0 equiv), *t*-BuOH–H_2O (1:1), 4 d, 91%, dr = 4:1.

A comparison of the specific rotation of compounds **4** and **22** in our work and those reported in the work of Trost et al. implies a pronounced improvement in enantiopurity by using the new synthetic approach (Scheme 6).



Scheme 6 Comparison of the specific rotations of compounds **4** and **22** obtained in the present work with those reported by Trost et al. *Reagents and conditions*: (a) DDQ (3.0 equiv), benzene, 80 °C, 2 h, 63%.

In summary, we have developed a short, efficient formal synthesis of (–)-siccanin (**1**) by using an enantioselective domino Wacker/carbonylation/methoxylation reaction to access chroman **11** and a two-step aldol condensation to install the pendent cyclohexyl moiety.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560752.

References and Notes

(1) (a) Ishibashi, K. J. *J. Antibiot., Ser. A* **1962**, *15*, 161. (b) Nozoe, S.; Suzuki, T.; Okuda, S. *Tetrahedron Lett.* **1968**, 3643. (c) Nozm, S.; Hirai, K. *Tetrahedron* **1971**, 6073. (d) Nozoe, S.; Hirai, K.; Snatzke, F.; Snatzke, G. *Tetrahedron* **1974**, *30*, 2773.
(2) (a) Nozoe, S.; Suzuki, K. T. *Tetrahedron* **1971**, *27*, 6063. (b) Hirai, K.; Nozoe, S.; Tsuda, K.; Iitaka, Y.; Shirasawa, M. *Tetrahedron Lett.* **1967**, 2177.
(3) (a) Kitano, N.; Kondo, F.; Kusano, K.; Ishibashi, K. US 397429, **1976**. (b) Matsuki, M.; Hanatsu, H.; Watanabe, T.; Ogasawara, A.; Mikami, T.; Matsumoto, T. *Biol. Pharm. Bull.* **2006**, *29*, 919. (c) Ishibashi, K.; Hirai, K.; Arai, M.; Sugasawa, S.; Endo, A.; Yasumura, A.; Matsuda, H.; Muramatsu, T. *Annu. Rep. Sankyo Res. Lab.* **1970**, *22*, 1.

(4) Belloti, M. G.; Riviera, L. *Chemioterapia: International Journal of the Mediterranean Society of Chemotherapy* **1985**, *4*, 431.
(5) Hirai, K.; Suzuki, K. T.; Nozoe, S. *Tetrahedron* **1971**, *27*, 6057.
(6) (a) Trost, B. M.; Shen, H. C.; Surivet, J. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3943. (b) Racemic:Kato, M.; Matsumura, Y.; Heima, K.; Fukamiya, N.; Kabuto, C.; Yoshikoshi, A. *Tetrahedron* **1987**, *43*, 711. (c) Racemic:Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146.
(7) Trost, B. M.; Shen, H. C.; Surivet, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 12565.
(8) Castillo, A.; Silva, L.; Briones, D.; Quílez del Moral, J. F.; Barrero, A. F. *Eur. J. Org. Chem.* **2015**, 3266.
(9) (a) Tietze, L. F.; Jackenkroll, S.; Hierold, J.; Ma, L.; Waldecker, B. *Chem. Eur. J.* **2014**, *20*, 8628. (b) Tietze, L. F.; Ma, L.; Reiner, J. R.; Jackenkroll, S.; Heidemann, S. *Chem. Eur. J.* **2013**, *19*, 8610. (c) Tietze, L. F.; Jackenkroll, S.; Raith, C.; Spiegl, D. A.; Reiner, J. R.; Ochoa-Campos, M. C. *Chem. Eur. J.* **2013**, *19*, 4876. (d) Tietze, L. F.; Wolfram, T.; Holstein, J. J.; Dittrich, B. *Org. Lett.* **2012**, *14*, 4035. (e) Tietze, L. F.; Stecker, F.; Zinngrebe, J.; Sommer, K. M. *Chem. Eur. J.* **2006**, *12*, 8770.
(10) *Domino Reactions: Concepts for Efficient Organic Synthesis*; Tietze, L. F., Ed.; Wiley-VCH: Weinheim, **2014**.
(11) **Experimental Procedure for the Preparation of (*R*)-5:** A solution of palladium(II) trifluoroacetate (48.2 mg, 145 µmol, 5 mol%) and the Bn-BOXAX ligand (*R*,*R*)-**10** (332 mg, 580 µmol, 20 mol%) in MeOH (10 mL) was stirred at r.t. for 15 min. Alkenyl phenol **7** (598 mg, 2.90 mmol, 1.00 equiv) in MeOH (7 mL) and *p*-benzoquinone (1.25 g, 11.6 mmol, 4.00 equiv) were added at r.t. and CO gas (1 atm) was passed through the resulting reaction mixture for 5 min. After stirring at r.t. under a CO atmosphere (1 atm) for 19 h, the reaction was quenched at r.t. by addition of 1 M aq HCl (50 mL). The aqueous phase was extracted with MTBE (3 × 25 mL) and the combined organic phases were washed with 1 M aq NaOH (3 × 25 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo. Column chromatography on silica gel (*n*-hexane–Et_2O 10:1→8:2) gave ester (*R*)-**5** (544 mg, 2.06 mmol, 71%, 95% ee) as a colorless oil; $[\alpha]_D$ = 8.2 (*c* = 0.50, $CHCl_3$, 24.0 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 3 H, 2'-CH_3), 1.85 (dt, *J* = 13.8, 6.8 Hz, 1 H, 3'-H_a), 1.99 (dt, *J* = 13.8, 6.8 Hz, 1 H, 3'-H_b), 2.26 (s, 3 H, 7'-CH_3), 2.55–2.66 (m, 4 H, 2-H_2, 4'-H_2), 3.68 (s, 3 H, 1-OCH_3), 3.79 (s, 3 H, 5'-OCH_3), 6.24, 6.29 (2 × s, 2 H, 6'-H, 8'-H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (C-4'), 21.5 (7'-CH_3), 24.6 (2'-CH_3), 30.3 (C-3'), 43.5 (C-2), 51.5 (1-OCH_3), 55.3 (5'-OCH_3), 74.2 (C-2'), 102.9, 110.4 (C-6', C-8'), 106.8 (C-4a'), 137.1 (C-7'), 153.5 (C-5'), 157.5 (C-8a'), 170.9 (C-1). IR (ATR): 2936, 2856, 1734, 1619, 1584, 1352, 1224, 1103, 1020, 811 cm^{-1}. UV (MeCN): λ_{max} (lg ε) = 208.0 (4.678), 272.0 (3.087) nm. Analytical HPLC (Daicel Chiracel OD; 4.6 × 250 mm, 5 µm, *n*-hexane–*i*-PrOH 98:2; 0.8 mL/min; 234 nm): t_R = 18.2 [(–)-(*S*)-**5**, 2.3%], 26.6 [(+)-(*R*)-**5**, 97.7%] min; 95% ee. MS (ESI): *m*/*z* (%) = 551.3 (99) [2M + Na]$^+$, 303.1 (11) [M + K]$^+$, 287.1 (100) [M + Na]$^+$, 265.2 (91) [M + H]$^+$. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{20}O_4$ (264.32): 265.1434; found: 265.1434; *m*/*z* [M + Na]$^+$ calcd: 287.1251; found: 287.1254.
(12) (a) Rubottom, G. M.; Mott, R. C. *J. Org. Chem.* **1979**, *44*, 1731. (b) Kharasch, M. S.; Tawney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308. (c) Reetz, M. T.; Kindler, A. *J. Organomet. Chem.* **1995**, *502*, C5.
(13) Olpp, T.; Brückner, R. *Angew. Chem. Int. Ed.* **2003**, *44*, 1610.
(14) Smith, A. B. III.; Nolen, E. G.; Shirai, R.; Blase, F. R.; Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, *60*, 7837.
(15) O'Grodnick, J. S.; Ebersole, R. C.; Wittstruck, T.; Caspi, E. *J. Org. Chem.* **1974**, *39*, 2124.
(16) Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.
(17) Tietze, L. F.; Krimmelbein, I. *Chem. Eur. J.* **2008**, *14*, 1541.