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# Enzyme- and Ruthenium-Catalyzed Dynamic Kinetic Asymmetric Transformation of 1,5-Diols. Application to the Synthesis of (+)-Solenopsin A

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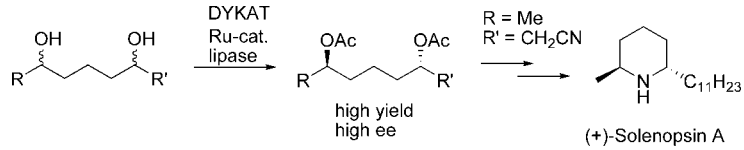


Dynamic kinetic asymmetric transformation (DYKAT) of 1,5-diols via combined lipase and ruthenium catalysis provides enantiomerically pure diacetates in high diastereoselectivity, which can serve as intermediates in natural product synthesis. This is demonstrated by the synthesis of (+)-Solenopsin A.

## Introduction

Ever since the first development of enzyme- and transition metal-catalyzed dynamic kinetic resolution (DKR) of secondary alcohols during the late 1990s,[1] the interest in this methodology has increased, and new catalysts have made the systems more robust and efficient.[2] This DKR method has also been extended to dynamic kinetic resolutions of primary alcohols[3] and amines.[4,5] When diols containing two chiral *sec*-alcohol centers are used in these systems, the method is classified as a dynamic kinetic asymmetric transformation (DYKAT).[6] Previously, both cyclic[7] and acyclic[8] 1,3-diols have been studied as well as 1,2-diols[9] and symmetrical 1,4-diols.[8b] In these cases, a diastereomeric diol mixture, containing pairs of enantiomers, can be transformed into one enantiopure diastereomer with a theoretical yield of 100% compared with the theoretical yield of ~25% obtained in an enzymatic kinetic asymmetric transformation (KAT) of the same substrates.

Chiral 1,5-diols are important synthetic intermediates, and there are examples in the literature where they are used in the synthesis of piperidine natural products.[10] We recently reported on the DYKAT of 1,5-diols,[11] where enantio- and diastereomerically enriched 1,5-diacetates were obtained, and herein we demonstrate their usefulness in the synthesis of (+)-Solenopsin A, a 2-methyl-6-alkylpiperidine.

## Results and Discussion

In our recent study of the enzyme- and ruthenium-catalyzed DYKAT of 1,5-diols, we found that diols **1a**−**1e** and **1g** (Figure 1) could be efficiently resolved into the corresponding enantiopure 1,5-diacetates in high yields and good diastereoselectivity (Table 1, entries 1−6 and 8).[11] The second-generation catalytic system[2b,12] proved to be the most efficient, and hence, catalyst **2** in combination with isopropenyl acetate as acyl donor and a

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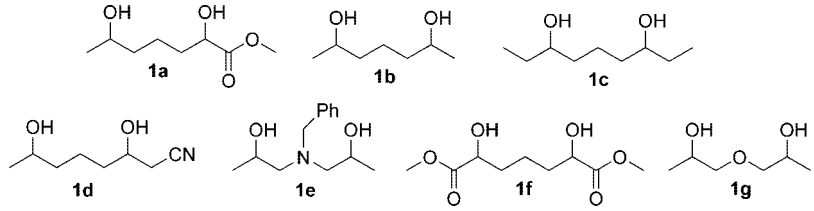
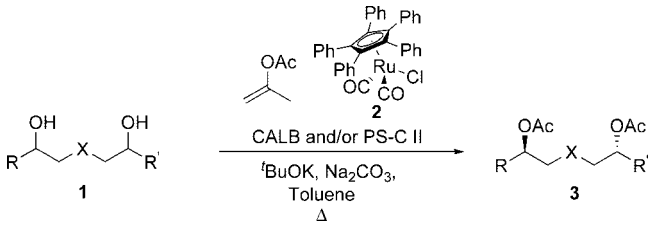



**FIGURE 1.** 1,5-Diols previously used in dynamic kinetic asymmetric transformation.

**TABLE 1. DYKAT of 1,5-Diols**[a]




| entry | diol | time (h) | temp (°C) | % ee[b] | *anti*:*syn*[b] | % yield[b,c] |
|---|---|---|---|---|---|---|
| 1 | **1a**[d,e,f] | 72 | 80 | 98 | 80:20 | 91 (71) |
| 2 | **1b** | 24 | 50 | >99 | 96:4 | 96 (80) |
| 3 | **1c**[f] | 48 | 50 | >99 | 94:6 | 96 (73) |
| 4 | **1c** | 40 | 50 | >99 | 96:4 | 89 |
| 5 | **1d**[e,f,g] | 40 | 100 | >99 | 94:6 | 83 (61) |
| 6 | **1e** | 48 | 50 | >99 | >99:1 | 99 (83) |
| 7 | **1f**[e,h] | 77 | 80 | 37 | 55:45 | 77 |
| 8 | **1g**[i] | 46 | 50 | >99 | 95:5 | 98 (81) |
| 9 | **1h**[j] | 48 | 50 | >99 | 94:6 | 85 (49) |
| 10 | **1i**[e,f,k] | 48 | 80 | 95 | 76:24 | 93 (78) |

[a] Unless otherwise stated, the reactions were performed on a 1 mmol scale in 1 mL of toluene with 3 equiv of isopropenyl acetate, 2.5−5 mg of CALB, 0.025 equiv of Ru-catalyst, 0.025 equiv of $^t$BuOK, and 1 mmol of $Na_2CO_3$ under argon. Compounds **1a**−**1g** and **3a**−**3g** are fully characterized in ref 11. [b] Determined by chiral GC. [c] Isolated yield in parentheses. [d] The reaction was run on a 2 mmol scale using 60 mg of CALB and 20 mg of PS-C II, where the latter was added after 5 h. [e] 6 equiv of isopropenyl acetate was used. [f] 0.05 equiv of Ru-catalyst and 0.05 equiv of $^t$BuOK in 2.5 mL of toluene. [g] 100 mg of CALB was used. [h] 0.05 equiv of Ru-catalyst, 10 mg of PS-C II, and 0.06 equiv of $^t$BuOK in 2.5 mL of toluene was used. [i] The reaction was run on a 5 mmol scale. [j] The reaction was run in 1.5 mL of toluene. [k] 30 mg of CALB was used, and 10 mg of PS-C II was added after 5 h.

lipase, CALB (*Candida antarctica* lipase B) or PS-C II (*Pseudomonas cepacia* lipase), was used.[13]

In the present paper, we have completed this series, studied the DYKAT of two additional substrates, **1h** and **1i** (Table 1, entries 9 and 10), and applied one of the enantiomerically pure diacetates in Table 1, **3d** (entry 5), to the synthesis of (+)-Solenopsin A. DYKAT of substrates **1h** and **1i** extends the generality of the method. In particular, enantiomerically pure diol derivatives of **1i** are useful since they readily allow functionalization at one end.

The syntheses of diols **1h** and **1i** are given in Scheme 1. Diol **1h** was prepared from 1,2-propanediol and 1-butenoxide according to a literature procedure.[14] Diol **1i** was obtained from the reaction of 1-butyn-2-ol and epichlorohydrin and the hydrogenation of the yne-diol **4** formed.

Diol **1i** was also prepared by a three-step synthesis starting from propylene oxide (Scheme 2). Although a third step was required, the reactions were cleaner and easier to purify. A second advantage with this route is that alcohol **5** and epoxide **6** also are intermediates in the synthesis of diol **1d**.[11]

The DYKAT of **1h** afforded diacetate **3h** in excellent enantio- and diastereoselectivity (Table 1, entry 9). In the DYKAT of **1i**, diacetate **3i** was obtained in 95% ee, but in a moderate *anti:syn* ratio (entry 10). Since aliphatic $\beta$-chlorohydrins are known to give poor enantioselectivity in lipase-catalyzed transesterification with PS-C II,[15] it was of interest to study this step separately for the diol. To investigate the enantioselectivity of the acylation of the alcohol next to the chloride in substrate **1i,** the appropriate diol monoacetate was prepared according to Scheme 3. Alcohol **5** was obtained, as described previously, from addition of 3-butenylmagnesium bromide to propylene oxide.[16] Subsequent kinetic resolution of **5** with CALB and isopropenyl acetate afforded the corresponding enantiomerically pure acetate (*R*)-**7**.[17] Epoxidation of (*R*)-**7** followed by chloride opening[18] afforded the requisite diol monoacetate (2*RS*,6*R*)-**9**.

Having obtained pure (2*RS*,6*R*)-**9**, we performed a KAT on this monoacetate using PS-C II and isopropenyl acetate to determine the enantioselectivity of the acylation of the alcohol next to the chloride. The reaction was run at 50 °C and to 26% conversion. The *anti*:*syn* ratio of the product was 97:3 which corresponds to a pseudo *E* value of 44 (Scheme 4).[19] This can be compared to the *E* value of 3.2 which was obtained for 1-chloro-2-nonanol.[15]

According to the determined pseudo *E* value, it should be possible to obtain diacetate **3i** in a higher diastereoselectivity than previously obtained in the DYKAT of **1i**. This was confirmed by performing a DYKAT of monoacetate (2*RS*,6*R*)-**9** which afforded diacetate (2*S*,6*R*)-**3i** in high enantioselectivity (>99% ee) and with an *anti:syn* ratio of 89:11 (Scheme 5).[20] The results show the importance of the 6-acetoxy group for the enzyme selectivity. Further improvement of the diastereoselectivity in the DYKAT may be possible by decreasing the enzyme loading, thereby assuring the epimerization to be fast enough.

Diacetate **3i** should be a useful intermediate for further synthetic transformations since the chloroacetate moiety can be transformed to epoxide in one step,[15] which in turn can be functionalized by ring opening. Also the diacetate products **3a** and **3d** allow further functionalization at one end: **3a** at the

(13) The use of two different enzymes in entry 1 of Table 1 (footnote d) is because CALB only reacts with the alcohol next to the methyl group and is essentially unreactive toward the alcohol next to the carboxy group. In this way, a selective acylation of the former alcohol group is obtained by using CALB in the beginning of the reaction (PS-C II gives a lower selectivity of that alcohol group). In the second step PS-C II is required since CALB stops after the first step.

(14) (a) Sexton, A. R.; Britton, E. C. *J. Am. Chem. Soc.* **1953**, *75*, 4357–4358. (b) Summerbell, R. K.; Jerina, D. M.; Grula, R. J. *J. Org. Chem.* **1962**, *27*, 4433–4436.

(15) Träff, A.; Bogár, K.; Warner, M.; Bäckvall, J.-E. *Org. Lett.* **2008**, *10*, 4807–4810.

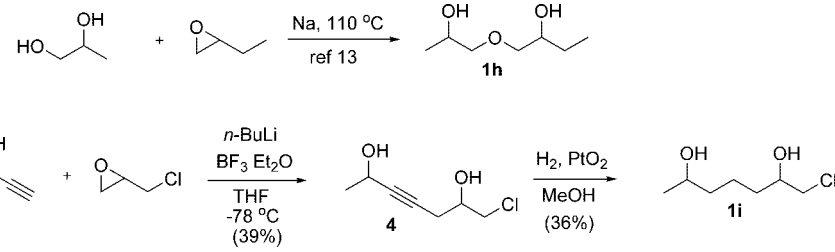
(16) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *Synthesis* **2005**, *13*, 2264–2266.

(17) When a DKR was performed with catalyst **2**, 82% conversion was obtained after 22 h, and the acetate showed an ee of 84%, indicating that the racemization has to be studied further.

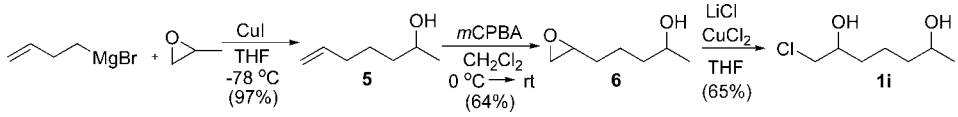
(18) Hoff, B. H.; Anthonsen, T. *Tetrahedron: Asymmetry* **1999**, *10*, 1401–1412.

(19) The reaction was run on a 0.2 mmol scale in 1 mL of toluene under argon, and a sample was taken after 2 h. Analysis by chiral CG showed 94% de (i.e., *anti*:*syn* = 97:3) of the product at 26% conversion. This corresponds to a pseudo *E* value of 44.

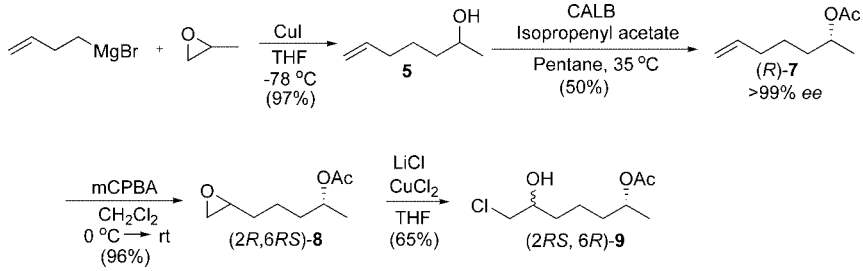
**SCHEME 1. Synthesis of New 1,5-Diols**



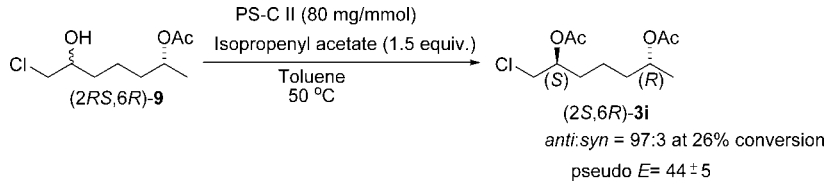

**SCHEME 2. Alternative Synthesis of Diol 1i**



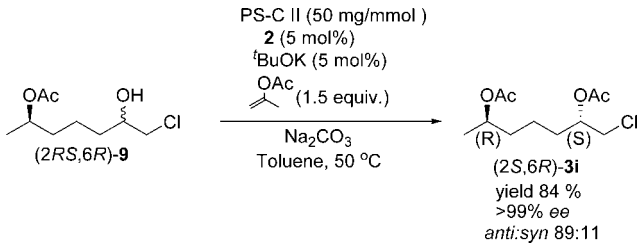

**SCHEME 3. Synthesis of Monoacetate (2*RS*,6*R*)-9**




**SCHEME 4. Determination of a Pseudo *E* Value for KAT of (2*RS*, 6*R*)-9**




**SCHEME 5. DYKAT of Monoacetate (2*RS*,6*R*)-9**




carboxyl group and **3d** at the cyano group. We have demonstrated the usefulness of one of these enantiomerically pure diacetates, **3d**, in natural product synthesis. Diacetate **3d** (Table 1, entry 4), which has a cyano group at one end, was transformed to (+)-Solenopsin A (**17**) in a few steps (Scheme 6). (+)-Solenopsin A (**17**) is the unnatural enantiomer of one of the constituents of the venom of the fire ant *Solenopsis invicta*.[21] Both enantiomers have been synthesized several times before,[10b,22] and diols **1a**, **1d**, and **1i** are potential starting materials for the synthesis of this *trans*-2,6-disubstituted piperidine. In Scheme 6 we have demonstrated how diol **1d** can be transformed to (+)-Solenopsin A via (3*S*,7*R*)-**3d**.

DYKAT of racemic diol **1d** using the conditions previously described[11] afforded diacetate (3*S*,7*R*)-**3d** in 67% isolated yield. The diacetate obtained was hydrolyzed into (3*S*,7*R*)-**1d** in 89% yield. The most straightforward route would be to form the piperidine ring first and then modify the side chain. Unfortunately, poor yields were obtained in the mesylation of optically pure (3*S*,7*R*)-**1d** due to elimination of the mesylate $\beta$ to the nitrile, which occurred rapidly. To circumvent this problem, the enantiomerically pure diol was protected with silyl groups prior to further modifications. Reduction of the nitrile group in **10** with DIBALH into the corresponding aldehyde **11**,[23] followed by a Wittig reaction[24] with (1-nonyl)triphenylphosphonium bromide, afforded **12.** Subsequent removal of the silyl protective groups and reduction of the double bond using Adam's catalyst[25] afforded diol **14**, which was transformed to dimesylate **15**.

(20) It is not clear why the DYKAT of diol **1i** gives such a poor diastereoselectivity, but one reason may be that the first acylation occurs to some extent on the alcohol next to the chloro group. Sequential use of enzymes CALB and PS-C II (added after 5 h) was employed since CALB reacts slowly with the chlorohydrin alcohol but fast with the alcohol next to the methyl group. However, the fact that DYKAT of the monoacetate (2*RS*,6*R*)-**9** gave only a diastereoselectivity of 89:11, in spite of the fact that the pseudo *E* value is 44 (and is expected to give a diastereoselectivity of 98:2 with an efficient epimerization), shows that there are other explanations. One obvious explanation is that the rate of epimerization is not fast enough. Another explanation is that some reversibility of the acylation reactions is occurring and this will lower the final isomeric purity of the product.

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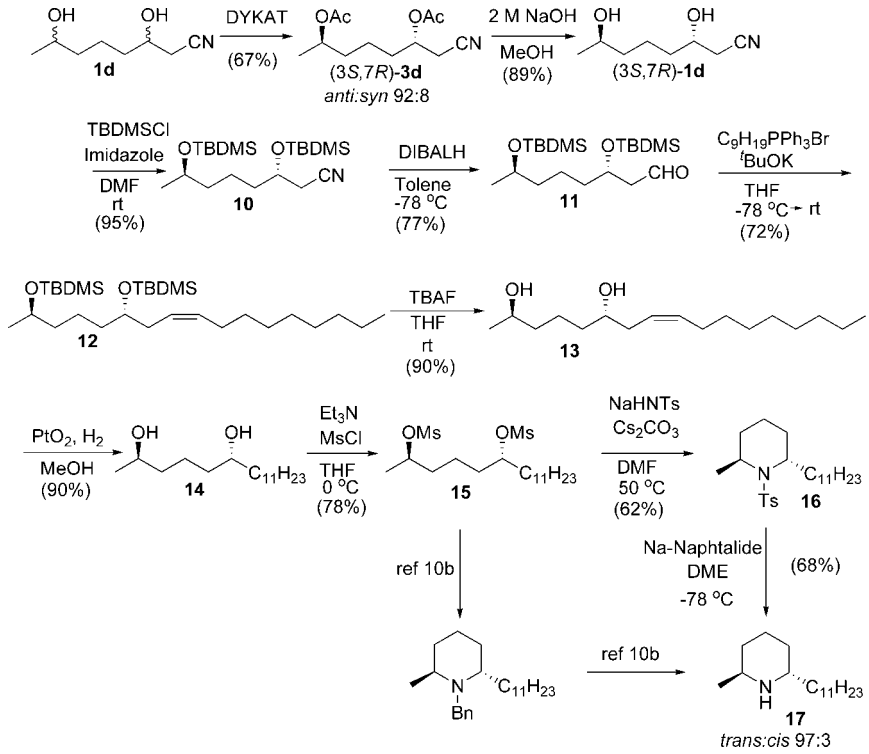
(23) Itoh, T.; Mitsukura, K.; Kanphai, W.; Takagi, Y.; Kihara, H.; Tsukube, H. *J. Org. Chem.* **1997**, *62*, 9165–9172.

**SCHEME 6. Synthesis of (+)-Solenopsin A from Diol 1d**




Dimesylate **15** had previously been transformed to Solenopsin A via reaction with benzylamine followed by debenzylation.[10b] However, we also chose an alternative pathway for formation of the piperidine ring through the reaction of dimesylate **15** with NaHNTs, since this method has proven to be efficient for intramolecular substitutions in our previous work.[11,26] Detosylation with sodium naphthalide[27] afforded (+)-Solenopsin A (**17**) in a total yield of 8% from diol **1d** ($[\alpha]^{22}_D$ +7.3 (*c* = 1.17, $CHCl_3$) for the HCl salt, lit.[22a] $[\alpha]^{22}_D$ +7.5 (*c* = 1.30, $CHCl_3$)), which was 97% *trans*.

## Conclusions

Dynamic kinetic asymmetric transformation of 1,5-diols is a powerful method for the synthesis of enantiomerically pure 1,5-diol derivatives. The utility of these diols as synthetic intermediates in natural product synthesis was demonstrated by the synthesis of (+)-Solenopsin A.

## Experimental Section

**DYKAT Reactions. (*R,R*)-2-Acetoxybutyl 2-Acetoxypropyl Ether (3h).** CALB (5 mg), $Na_2CO_3$ (106 mg, 1 mmol), and ruthenium catalyst **2** (16 mg, 0.025 mmol) were put in a flame-dried Schlenk tube under argon. Then toluene (1 mL) and $^t$BuOK (0.5 M in THF; 50 $\mu$L, 0.025 mmol) were added. The reaction was lowered into an oil bath preheated to 50 °C, and after 6 min diol **1h** (157 mg, 1 mmol) was added. After another 4 min isopropenyl acetate (330 $\mu$L, 3 mmol) was added. The mixture was left stirring at 50 °C for 48 h and then filtered and concentrated. Purification by chromatography (pentane:EtOAc 4:1 to EtOAc) afforded (2*R*,6*R*)-**3h** (114 mg, 49%) as an oil. The ee and diastereomeric ratio were determined by chiral GC: >99% ee, *anti:syn* = 94:6. $[\alpha]^{22}_D$ +19.1 (*c* = 1.0, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.90 (t, *J* = 7.4 Hz, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.52−1.69 (m, 2H), 2.04 (s, 3H), 2.06 (s, 1H), 3.42 (dd, *J* = 10.5, 4.3 Hz, 1H), 3.48 (dd, *J* = 10.8, 4.1 Hz, 1H), 3.54 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.56 (dd, *J* = 10.8, 6.0 Hz), 4.92 (m, 1H), 5.04 (ddq, *J* = 6.5, 6.3, 4.3, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 9.5, 16.5, 21.1, 21.2, 23.8, 69.2, 72.0, 73.5, 73.7, 170.5, 170.7.

**(2*S*,6*R*)-2,6-Diacetoxy-1-chloroheptane (3i).** PS-C II (50 mg), $Na_2CO_3$ (106 mg, 1 mmol), and ruthenium catalyst **2** (32 mg, 0.05 mmol) were put in a flame-dried Schlenk tube under argon. Toluene (1.5 mL) and $^t$BuOK (0.5 M in THF; 100 $\mu$L, 0.05 mmol) were added. The reaction was lowered into an oil bath preheated to 50 °C, and after 6 min monoacetate **6** (209 mg, 1 mmol) dissolved in 0.5 mL toluene was added. After another 4 min, isopropenyl acetate (165 $\mu$L, 1.5 mmol) was added, and the mixture was left stirring at 50 °C for 18 h. The mixture was cooled to rt and purified by chromatography without filtration or evaporation (pentane, then pentane:$Et_2O$ 9:1) to afford (2*R*,6*R*)-**3i** (212 mg, 84%) as an oil. The ee and diastereomeric ratio were determined by chiral GC: >99% ee, *anti:syn* = 89:11. $[\alpha]^{22}_D$ −6.8 (*c* = 1.0, EtOAc). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.96 (d, *J* = 6.3 Hz, 3H), 1.30−1.71 (m, 6H), 2.02 (s, 3H), 2.08 (s, 3H), 3.55 (dd, *J* = 11.6, 5.3 Hz), 3.60 (dd, *J* = 11.6, 4.7 Hz, 1H), 4.87 (m, 1H), 5.01 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 19.9, 20.9 (2 C), 21.3, 31.2, 35.5, 45.5, 70.5, 72.6, 170.4, 170.7. HRMS (ESI) (M + Na)$^+$: *m/z* calcd for $C_{11}H_{19}ClNaO_4$ 273.0864, obsd 273.0857.

**Synthesis of (+)-Solenopsin A. (3*S*,7*R*)-3,7-Diacetoxyoctanenitrile ((3*S*,7*R*)-3d).** CALB (100 mg), $Na_2CO_3$ (106 mg, 1 mmol), and ruthenium catalyst **2** (32 mg, 0.05 mmol) were placed in a flame-dried Schlenk tube under argon. Then toluene (2.5 mL) and $^t$BuOK (0.5 M in THF; 100 $\mu$L, 0.05 mmol) were added. The reaction was lowered into an oil bath preheated to 100 °C, and after 6 min diol **1d** (157 mg, 1 mmol) was added. After another 4 min, isopropenyl acetate (660 $\mu$L, 6 mmol) was added, and the mixture was left stirring at 100 °C for 48 h. The mixture was then

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filtered and concentrated. Two similar reactions were started, and the combined crude products were purified by chromatography (pentane:$Et_2O$ 4:1 to $Et_2O$) to afford (3*S*,7*R*)-**3d** (321 mg, 67%) as an oil. The ee and diastereomeric ratio were determined by chiral GC: >99% ee, *anti:syn* = 92:8. Analytical data agreed with those previously reported.[11]

**(3*S*,7*R*)-3,7-Dihydroxyoctanenitrile ((3*S*,7*R*)-1d).**[28] A 2 M NaOH solution (aq) (1.58 mL, 3.2 mmol) was added to a solution of (3*S*,7*R*)-**3** (255 mg, 1.06 mmol) in 26 ml of MeOH. The resulting mixture was stirred at rt for 40 min. MeOH was evaporated, and the residue was dissolved in sat. NaCl (aq) and extracted several times with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated yielding the title compound (147 mg, 89%), which was used without further purification. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 1.20 (3H, d, $J$ = 6.2 Hz, $CH_3$), 1.39−1.70 (6H, m, 3 × $CH_2$), 2.50 (ABX, $J_{AB}$ = 16.6 Hz, $J_{AX}$ = 5.1 Hz, 1H), 2.56 (ABX, $J_{AB}$ = 16.6 Hz, $J_{BX}$ = 6.3 Hz, 1H), 3.83 (1H, m, CH), 3.95 (1H, m, CH). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 21.5, 23.8, 26.2, 36.1, 38.2, 67.4, 67.8, 117.8.

**(3*S*,7*R*)-3,7-Bis(*tert*-butyldimethylsilyloxy)octanenitrile (10).** (3*S*,7*R*)-**1d** (147 mg, 0.93 mmol) was dissolved in 2 mL of dry DMF and cooled to 0 °C. A solution of TBDMS−Cl (562 mg, 3.7 mmol) in 2 mL of dry DMF was added followed by imidazole (254 mg, 3.7 mmol) dissolved in 2 mL of dry DMF. The resulting mixture was stirred at room temperature for 2 days. Then water was added and the mixture was extracted three times with $Et_2O$. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by chromatography (pentane:$Et_2O$ 95:5) afforded **10** (344 mg, 95%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.04, (s, 3H), 0.05 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 0.90 (s, 3H), 1.11 (d, $J$ = 6.0, 3H), 1.24−1.70 (m, 6H), 2.42 (ABX, $J_{AB}$ = 16.5 Hz, $J_{AX}$ = 5.5 Hz, 1H), 2.47 (ABX, $J_{AB}$ = 16.5 Hz, $J_{BX}$ = 5.7 Hz, 1H), 3.78 (m, 1H), 3.93 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ −4.7 (2 C), −4.6, −4.4, 17.9, 18.1, 21.2, 23.8, 25.7, 25.9, 26.1, 37.2, 39.6, 68.3, 68.4, 117.8. HRMS (ESI) (M + Na)$^+$: *m*/*z* calcd for $C_{20}H_{43}NNaO_2Si_2$ 408.2725, obsd 408.2707.

**((3*S*,7*R*)-3,7-Bis(*tert*-Butyldimethylsilyloxy)octanal (11).** A solution of **10** (325 mg, 0.84 mmol) in 14 mL of dry toluene was cooled to −78 °C. DIBALH (1.26 mL, 1 M in toluene, 1.26 mmol) was added dropwise, and the resulting mixture was stirred at −78 °C under argon. After 4 h, 5 mL of water containing 0.9 g of $SiO_2$ powder was added, and the mixture was stirred at room temperature for another 30 min. The solid was filtered off, and the mixture was extracted with $Et_2O$ three times. The combined organic layers were dried over $MgSO_4$ and evaporated. Purification by chromatography (pentane:$Et_2O$ 95:5) afforded **11** (253 mg, 77%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.04 (s × 2, 3H × 2), 0.05 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.88 (s, 9H), 1.11 (d, $J$ = 6.1 Hz, 3H), 1.24−1.61 (m, 6H), 2.51 (m, 2H), 3.77 (m, 1H), 4.18 (m, 1H), 9.81 (t, $J$ = 2.5 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ −4.7 (2 C), −4.4 (2 C), 18.0, 18.1, 21.4, 23.8, 25.8, 25.9, 38.0, 39.8, 50.8, 68.3, 68.4, 202.4. HRMS (ESI) (M + Na)$^+$: *m*/*z* calcd for $C_{20}H_{44}NaO_3Si_2$ 411.2721, obsd 411.2709.

**(2*R*,6*S*)-2,6-Bis(*tert*-butyldimethylsilyloxy)-8-heptadecene (12).** $^t$BuOK (55 mg, 0.49 mmol) was dissolved in 3 mL of dry THF and cooled to −78 °C. (1-Nonyl)triphenylphosphonium bromide (230 mg, 0.49 mmol) was added, and the resulting orange mixture was stirred for 20 min. A solution of **11** in 1 mL of dry THF was added slowly, and the yellow mixture was stirred at −78 °C for 2 h then for another hour at room temperature. Brine was added, and the mixture was extracted with three portions of $Et_2O$. The combined organic layers were dried over $MgSO_4$ and evaporated. Purification by chromatography (pentane:$Et_2O$ 98:2) afforded the title compound (135 mg, 72%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.04 (2*s*, 2 × 6H), 0.88 (s, 9H), 0.89 (s, 9H), 1.11 (d, $J$ = 6.1 Hz), 1.22−1.47 (m, 18H), 2.01 (m, 2H), 2.19 (m, 2H), 3.65 (m, 1H), 3.77 (m, 1H), 5.40 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ −4.7, −4.5, −4.4, −4.3, 14.1, 18.1 (2 C), 21.9, 22.7, 23.8, 25.9, 27.5, 29.3, 29.4, 29.5, 29.7, 31.9, 35.3, 37.1, 40.1, 68.7, 72.4, 125.8, 131.5. HRMS (ESI) (M + Na)$^+$: *m*/*z* calcd for $C_{29}H_{62}NaO_2Si_2$ 521.4181, obsd 521.4189.

**(2*R*,6*S*)-2,6-Dihydroxy-8-heptadecene (13).** To a solution of **12** (131 mg, 0.26 mmol) in 2 mL of dry THF was added TBAF (413 mg, 1.58 mmol) dissolved in 2 mL of dry THF. The resulting mixture was stirred under argon for 2.5 days, and then $NH_4Cl$ (aq) was added. The mixture was extracted several times with EtOAc, and the combined organic layers were dried over $MgSO_4$ and evaporated. Purification by chromatography (pentane:EtOAc 2:1 to EtOAc) afforded diol **13** (64 mg, 90%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.20 (d, $J$ = 6.3 Hz, 3H), 1.23−1.54 (m, 18 H), 1.62 (br s, 2H), 2.05 (app. q, $J$ = 7.3 Hz, 2H), 2.22 (app. t, $J$ = 6.9, 2H), 3.63 (m, 1H), 3.81 (m, 1H), 5.39 (m, 1H), 5.57 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 22.0, 22.7, 23.6, 27.4, 29.3, 29.5, 29.7, 31.9, 35.5, 36.6, 39.1, 68.0, 71.3, 124.9, 133.7.

**(2*R*,6*S*)-2,6-Heptadecanediol (14).** Diol **13** (63 mg, 0.23 mmol) was dissolved in 1.5 mL of MeOH, and $PtO_2$ (2.1 mg, 0.009 mmol) was added. The flask was evacuated and filled with argon, then evacuated again. A balloon filled with $H_2$(g) was attached to the flask. The flask was filled with $H_2$, and the mixture was stirred under $H_2$ (1 atm) for 4.5 h. The flask was evacuated and filled with argon, and the mixture was filtered through silica and rinsed with EtOAc. Evaporation of the solvent afforded **14** (61 mg, 90%) which was used without further purification. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.88 (t, $J$ = 6.8 Hz, 3H), 1.19 (d, $J$ = 6.3 Hz, 3H), 1.22−1.52 (m, 24H), 3.60 (m, 1H), 3.81 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 21.8, 22.7, 23.6, 25.7, 29.3, 29.6 (4 C), 29.7, 31.9, 37.2, 37.6, 39.1, 68.0, 71.8.

**(2*R*,6*S*)-2,6-Dimesylheptadecane (15).** Diol **14** (51.5 mg, 0.19 mmol) was dissolved in 3 mL of dry THF and cooled to 0 °C. $Et_3N$ (63 $\mu$L, 0.45 mmol) was added followed by a dropwise addition of MsCl (35 $\mu$L, 0.45 mmol). The resulting mixture was stirred at 0 °C for 1.5 h, and water was added. The aqueous phase was extracted with $Et_2O$, and the combined organic phases were dried over $MgSO_4$ and evaporated. Purification by chromatography (pentane:EtOAc 2:1 to EtOAc) afforded the title compound (63.2 mg, 78%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.22−1.38 (m, 18H), 1.42 (d, $J$ = 6.3 Hz, 3H), 1.48−1.82 (m, 8H), 3.01 (s, 6H), 4.70 (m, 1H), 4.80 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 20.7, 21.2, 22.7, 25.0, 29.3 (2 C), 29.4, 29.5, 29.6, 31.9 (2 C), 33.9, 34.6, 36.2, 38.6, 38.7, 79.6, 83.5.

**(*S*,*S*)-2-Methyl-6-undecyl-1-(toluene-4-sulfonyl)-piperidine (16).** Dimesylate **15** (61.2 mg, 0.14 mmol) was dissolved in dry DMF (2 mL), and NaHNTs (82.8 mg, 0.43 mmol) and $Cs_2CO_3$ (46.5 mg, 0.14 mmol) were added. The resulting mixture was heated at 50 °C for 5 days and was allowed to cool to rt. Water was added, and the mixture was extracted with $Et_2O$. The organic phases were washed with water and brine, dried over $MgSO_4$, and evaporated. Purification by chromatography (pentane:$Et_2O$ 9:1 to $Et_2O$) afforded **16** (36 mg, 62%). $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 0.88 (t, $J$ = 7.0 Hz, 3H), 1.23 (d, $J$ = 7.0 Hz, 3H), 1.23−1.79 (m, 26 H), 2.40 (s, 3H), 3.60 (m, 1H), 4.15 (m, 1H), 7.24 (m, 2H), 7.71 (m, 2H). $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 14.1, 19.3, 20.2, 21.4, 22.7, 26.9, 28.1, 29.3, 29.5, 29.6 (3 C), 29.7, 31.0, 31.9, 32.8, 50.5, 55.6, 127.0, 129.3, 141.7, 142.3.

**(+)-Solenopsin A (17).** Sodium (9 mg, 0.39 mmol) was added to a solution of naphthalene (50 mg, 0.39 mmol) in 1 mL of DME, and the mixture was stirred at rt for 30 min. The resulting dark green mixture was cooled to −78 °C, and **16** (26 mg, 0.064 mmol) in 0.5 mL of DME was added dropwise. After stirring for 1 h at −78 °C, brine was added, and the reaction was warmed to rt. The mixture was extracted with EtOAc × 3, and the combined organic phases were dried over $Na_2SO_4$ and evaporated. Purification by chromatography ($CH_2Cl_2$:MeOH:$NH_4OH$ 90:10:1) afforded (+)-Solenopsin A (**17**) (11 mg, 68%) as a pale yellow oil. NMR data

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agreed with those reported in the literature.[29] $[\alpha]^{22}_{D}$ +7.3 ($c$ = 1.17, $CHCl_3$) for the HCl salt, lit.[22a] $[\alpha]^{22}_{D}$ +7.5 ($c$ = 1.30, $CHCl_3$).

**Absolute Configuration of Chiral Compounds.** The absolute configuration of compounds **3a**−**3h** was established in ref 11. The absolute configuration of compounds (3*S*,7*R*)-**1d**, **10**, **11**, **12**, **13**, **14**, **15**, and **16** follows from the configuration of (3*S*,7*R*)-**3d**, since (3*S*,7*R*)-**1d**, **10**, and **11** are derivatives of (3*S*,7*R*)-**3d**, **12**, **13**, **14**, **15**, and **16**, which are obtained from **11** without changing the chiral center. The absolute configuration of (3*S*,7*R*)-**1d**, **10**, **11**, **12**, **13**, **14**, **15**, and **16** was confirmed by their transformation to the known **17** ((+)-Solenopsin). The absolute configuration of the latter compound (**17**) was established by the sign of the optical rotation (see above). Compound (*R*)-**7** was prepared according to a literature procedure which was reported to give the (*R*)-configuration.[30] The absolute configuration of (2*R*,6*RS*)-**8** and (2*RS*,6*R*)-**9** follows from the configuration of (*R*)-**7**. The absolute configuration of (2*S*,6*R*)-**3i** follows from the fact that the 6*R* configuration is established through (*R*)-**7**, and that the acylation of chlorohydrins are known to give the (*S*)-configuration according to ref 15, which is consistent with Kazlauskas' rule.[31] The absolute configuration of compound (2*R*,6*R*)-**3h** was assigned on the bassis of the known absolute configuration of (2*R*,6*R*)-**3g**, which was established in ref 11. Both compounds follow Kazlauskas' rule[31] and differ only in that one terminal methyl (**3h**) is replaced by a terminal ethyl (**3g**).

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**Supporting Information Available:** General methods. Preparation of diols and copies of $^1H$ and $^{13}C$ NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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