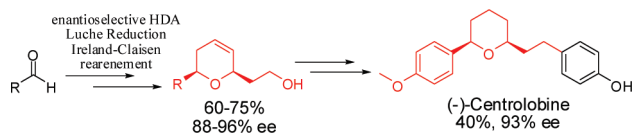


**Enantioselective Construction of
Cis-2,6-Disubstituted Dihydropyrans: Total
Synthesis of (–)-Centrolobine**Wojciech Chaładaj,[†] Rafał Kowalczyk,[‡] and
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This paper presents a simple and efficient route to chiral *cis*-6-substituted 2-(2-hydroxyethyl)-5,6-dihydro-2*H*-pyrans, a versatile chiral building block. The strategy is based on three key transformations: enantioselective hetero-Diels–Alder (HDA) reaction of aldehyde with Danishefsky's diene, selective reduction of carbonyl function, and Claisen or related rearrangement. The synthetic utility of the methodology is illustrated by total synthesis of antibiotic (–)-centrolobine.

The tetrahydropyran moiety is a common motif in a number of natural and synthetic compounds possessing biological activity.¹ Although the oxo-Diels–Alder reaction

seems to be the most straightforward route to such 6-membered rings, this approach is relatively rarely employed.² This fact can be attributed to the necessity to ensure not only high enantioselectivity but also diastereoselectivity of cycloaddition. Moreover, syntheses of properly substituted sophisticated dienes could be challenging and thus discourage use of the Diels–Alder strategy. For instance, out of 18 reported total syntheses of (–)-centrolobine,³ only one is based on the Diels–Alder reaction strategy.⁴

Herein, we present an efficient and highly enantioselective route to *cis*-6-substituted 2-(2-hydroxyethyl)-5,6-dihydro-2*H*-pyrans **1**, useful building blocks (Scheme 1).⁵ The strategy is based on three key transformations: enantioselective hetero-Diels–Alder (HDA) reaction⁶ of an aldehyde with Danishefsky's diene, a highly selective reduction of carbonyl function, and the Claisen or related rearrangement.⁷ Stable and well-defined salen chromium complexes are the catalysts of choice for the enantioselective HDA reaction.⁸ In particular, the easily accessible sterically modified salen complex **2** (Figure 1)^{9,10} was shown to catalyze cycloaddition of Danishefsky's diene **3** to various aldehydes **4** in high yields and enantioselectivities.¹⁰ Furthermore, Luche reduction¹¹ is a well-established procedure for the conversion of the pyranones of type **5** to the corresponding allyl alcohols **6** in a completely *cis*-selective fashion.¹² The alcohol **6** was acetylated to produce ester **7**, which was subjected to the Ireland–Claisen rearrangement.¹³ Notably, all transformations (namely: reduction, acetylation, and rearrangement)

(4) Washio, T.; Yamaguchi, R.; Abe, T.; Nambu, H.; Anada, M.; Hashimoto, S. *Tetrahedron* **2008**, *63*, 12037.

(5) For examples, see: (a) Bhattacharjee, A.; Soltani, O.; De Brabander, J. K. *Org. Lett.* **2002**, *4*, 481. (b) Paterson, I.; Anderson, E. A.; Dalby, S. M.; Loiseleur, O. *Org. Lett.* **2005**, *7*, 4125. (c) Kang, E. J.; Cho, E. J.; Lee, Y. E.; Ji, M. K.; Shin, D. M.; Chung, Y. K.; Lee, E. *J. Am. Chem. Soc.* **2004**, *126*, 2680. (d) Kang, E. J.; Cho, E. J.; Ji, M. K.; Lee, Y. E.; Shin, D. M.; Choi, S. Y.; Chung, Y. K.; Kim, J.-S.; Kim, H. -J.; Lee, S. -G.; Lah, M. S.; Lee, E. *J. Org. Chem.* **2005**, *70*, 6321.

(6) For a representative review on the HDA, see: (a) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2398. (b) *Cycloaddition Reaction in Organic Synthesis*; Kobayashi, S.; Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002.

(7) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939.

(8) (a) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (b) Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845. (c) Michara, J.; Aikawa, K.; Uchida, T.; Irie, R.; Katsuki, T. *Heterocycles* **2001**, *54*, 395. (d) Kwiatkowski, P.; Asztemborska, M.; Caille, J.-C.; Jurczak, J. *Adv. Synth. Catal.* **2003**, *345*, 506. (e) Kosior, M.; Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2897. (f) Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Synlett* **2004**, 1755. (g) Malinowska, M.; Kwiatkowski, P.; Jurczak, J. *Tetrahedron Lett.* **2004**, *45*, 7693. (h) Kwiatkowski, P.; Chaładaj, W.; Malinowska, M.; Asztemborska, M.; Jurczak, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2959. (i) Chaładaj, W.; Kwiatkowski, P.; Jurczak, J. *Synlett* **2006**, 3263. (j) Berkesel, A.; Vogel, N. *Eur. J. Org. Chem.* **2006**, 5029.

(9) (a) Kwiatkowski, P.; Chaładaj, W.; Jurczak, J. *Synlett* **2005**, 2301. (b) Kowalczyk, R.; Kwiatkowski, P.; Skarzewski, J.; Jurczak, J. *J. Org. Chem.* **2009**, *74*, 753.

(10) Chaładaj, W.; Kwiatkowski, P.; Jurczak, J. *Tetrahedron Lett.* **2008**, *49*, 6810.

(11) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(12) For representative examples, see: (a) Gołębowski, A.; Kozak, J.; Jurczak, J. *J. Org. Chem.* **1991**, *56*, 7344. (b) Paterson, I.; Smith, J. D. *J. Org. Chem.* **1992**, *57*, 3261. (c) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518. (d) Potuzak, J. S.; Moilanen, S. B.; Tan, D. S. *J. Am. Chem. Soc.* **2005**, *114*, 13796.

(13) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(1) For representative examples, see: (a) Morris, J. C.; Phillips, A. J. *Nat. Prod. Rep.* **2009**, *25*, 95. (b) Nicolaou, K. C.; Synder, S. A. *Classics in Total Synthesis*; Wiley-VCH: Weinheim, 2003. (c) Smith, A. B. III; Fox, R. J.; Razler, T. M. *Acc. Chem. Res.* **2008**, *41*, 675.

(2) For a brief summary of strategies for construction of tetrahydropyran ring, see: Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045.

(3) (a) Colobert, F.; Mazery, R. D.; Solladie, G.; Carreno, M. C. *Org. Lett.* **2002**, *4*, 1723. (b) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (c) Carreno, M. C.; Mazery, R. D.; Urbano, A.; Colobert, F.; Solladie, G. *J. Org. Chem.* **2003**, *68*, 7779. (d) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883. (e) Lee, E.; Kim, H. J.; Jang, W. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1609. (f) Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadere, B. *Tetrahedron Lett.* **2004**, *45*, 6603. (g) Clarke, P. A.; Martin, W. H. C. *Tetrahedron Lett.* **2004**, *45*, 9061. (h) Chan, K. P.; Loh, T. P. *Org. Lett.* **2005**, *7*, 4491. (i) Clarke, P. A.; Martin, W. H. C. *Tetrahedron* **2005**, *61*, 5433. (j) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46*, 2021. (k) Chandrasekhar, S.; Prakash, S. J.; Shyamsunder, T. *Tetrahedron Lett.* **2005**, *46*, 6651. (l) Bohrsch, V.; Bleichert, S. *Chem. Commun.* **2006**, 1968. (m) Lee, C. H. A.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 1641. (n) Prasad, K. R.; Anbarasan, P. *Tetrahedron* **2007**, *63*, 1089. (o) Dziedzic, M.; Furman, B. *Tetrahedron Lett.* **2008**, *49*, 678. (p) Takeuchi, T.; Matsuhashi, M.; Nakata, T. *Tetrahedron Lett.* **2008**, *49*, 6462. (r) Zhou, H.; Loh, T. P. *Tetrahedron Lett.* **2009**, *50*, 4368. (s) He, A. Y.; Sutivisedsak, N.; Spilling, C. D. *Org. Lett.* **2009**, *11*, 3124.

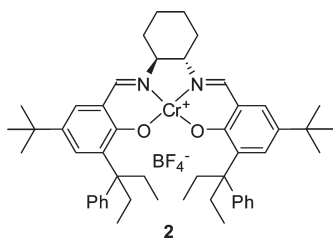
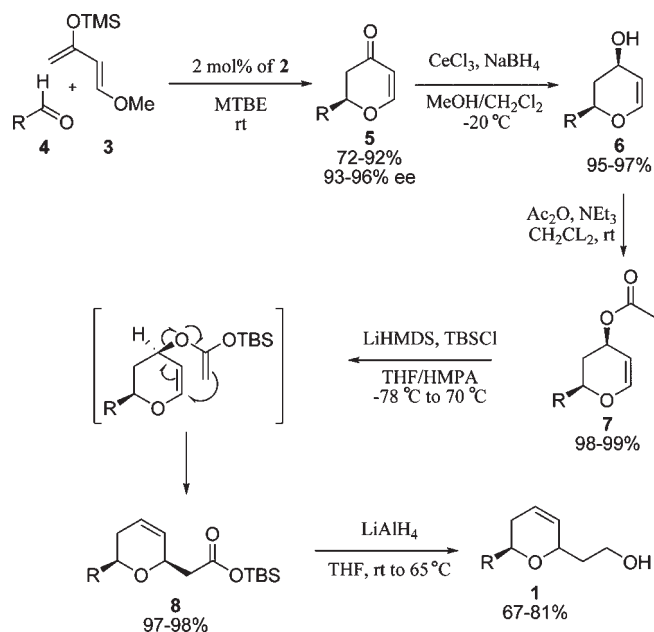


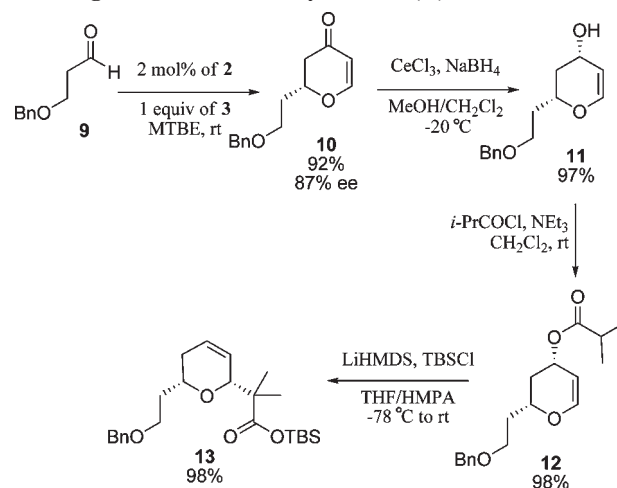
FIGURE 1. Sterically modified (salen)Cr complex.

SCHEME 1. Synthetic Route to *Cis*-6-Substituted 2-(2-Hydroxyethyl)-5,6-dihydro-2*H*-pyrans **1**

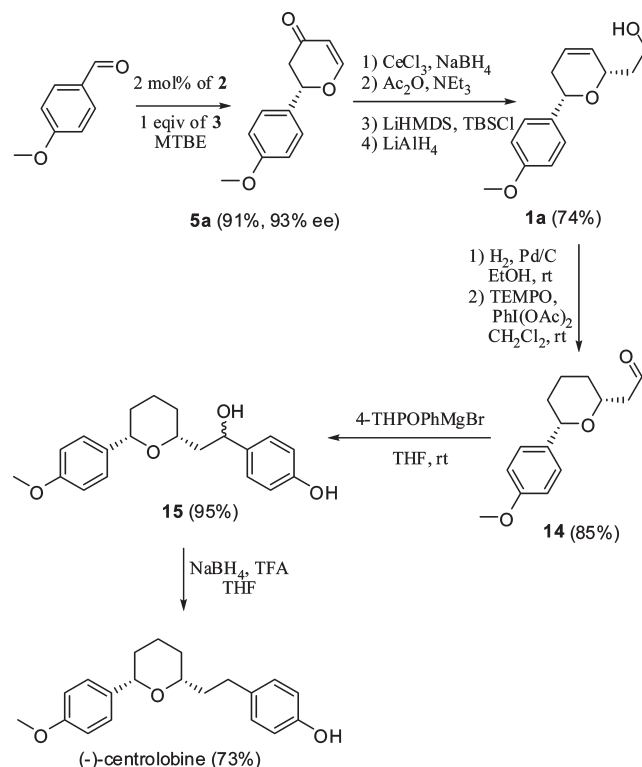
were almost quantitative; after typical extractive workup, the reaction products were sufficiently pure for further transformations. Finally, the silyl ester **8** was reduced, yielding the desired *cis*-6-substituted 2-(2-hydroxyethyl)-5,6-dihydro-2*H*-pyran **1**, which could be hydrogenated to a tetrahydropyran or further functionalized at the double bond and the hydroxy group.

Aldehydes **4a–c** were converted to the dihydropyrans **1a–c** in overall yields and enantioselectivities exceeding 45% yield and 90% ee, respectively. In the case of the least reactive anisaldehyde, application of 1.5 equiv of Danishefsky's diene was necessary to ensure high reaction yield; under standard reaction conditions (1 equiv of diene), the resulting pyranone was formed in only 61% yield.

The methodology is not limited to the rearrangement of acetates. In order to show its potential, (*R*)-2-(2-(benzyloxy)ethyl)-2*H*-pyran-4(3*H*)-one **10**, obtained in the HDA reaction from 3-benzyloxypropionaldehyde **9**, was subsequently reduced to alcohol **11**, converted to the isobutyrate **12**, and subjected to the Ireland–Claisen rearrangement (Scheme 2).

SCHEME 2. Synthetic Route to the Protected 2-((2*R*,6*S*)-6-(2-Hydroxyethyl)-5,6-dihydro-2*H*-pyran-2-yl)-2-methylpropanoic Acid: A Building Block Useful in the Synthesis of (+)-SCH 351448

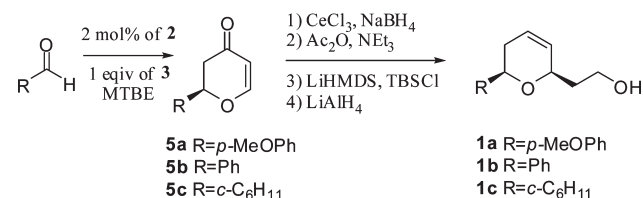
SCHEME 3. Synthesis of (–)-Centrolobine



The silyl ester **13** was isolated after three steps from **10** in 91% as a sole product employing only extractions but no chromatography at any step. The compound **13** is an interesting building block that can be utilized in the total synthesis of (+)-SCH 351448, a low density lipoprotein receptor promoter.^{5c,d,14} To the best of our knowledge, none of the reported total syntheses methods of (+)-SCH 351448 employed the HDA reaction for the construction of tetrahydropyran rings.

Finally, the aforementioned methodology was employed to the total synthesis of (–)-centrolobine (Scheme 3). Dihydropyran **1a**, obtained from anisaldehyde in 67% yield and

(14) (a) Cheung, L. L.; Marumoto, S.; Anderson, C. D.; Rychnovsky, S. D. *Org. Lett.* **2008**, *10*, 3101. (b) Chan, K.-P.; Ling, Y. H.; Loh, T.-P. *Chem. Commun.* **2007**, 939. (c) Chan, K.-P.; Ling, Y. H.; Chan, J. L. T.; Loh, T.-P. *J. Org. Chem.* **2005**, *70*, 6321. (d) Crimmins, M. T.; Vanier, G. S. *Org. Lett.* **2006**, *8*, 2887. (e) Backes, J. R.; Koert, U. *Eur. J. Org. Chem.* **2006**, 2777. (f) Soltani, O.; De Brabander, J. K. *Org. Lett.* **2005**, *7*, 2791. (g) Bolshakov, S.; Leighton, J. L. *Org. Lett.* **2005**, *7*, 3809.

TABLE 1. Synthesis of the *Cis*-6-Substituted 2-(2-Hydroxyethyl)-5,6-dihydro-2*H*-pyrans

entry	R	yield of 5 (%)	yield of 5 → 1 (%)	ee (%)
1	<i>p</i> -MeOPh	91	74	93 ^a
2	Ph	92	71	94 ^b
3	<i>c</i> -C ₆ H ₁₁	72	63	96 ^b

^aDetermined by HPLC on a chiral OD-H column. ^bDetermined by GC on a chiral capillary β -dex 120 column.

93% ee (Table 1, entry 2), was hydrogenated to the corresponding tetrahydropyran. A short reaction time and the use of ethyl acetate as a solvent were crucial to prevent the destruction of the tetrahydropyran ring; the reaction carried out in methanol afforded exclusively the product of subsequent hydrogenolysis of the tetrahydropyran ring. The product of hydrogenation of **1a** was oxidized to the aldehyde **14** which was then subjected to reaction with THP-protected 4-hydroxyphenylmagnesium bromide. An acidic workup of the reaction mixture resulted in deprotection of the phenolic hydroxy function, yielding the alcohol **15** in 91% yield. Removal of the hydroxy group at the benzylic position was accomplished with a combination of NaBH₄ and TFA in THF,¹⁵ producing (–)-centrolobine in 73%, with spectral data and optical rotation in agreement with those reported in the literature.^{3,4} Starting from anisaldehyde, (–)-centrolobine was achieved in nine steps only (five of which required chromatographic purifications) in 40% overall yield and with enantiomeric purity of 93% ee.

In conclusion, a simple and efficient enantioselective route to the versatile building blocks such as *cis*-6-substituted 2-(2-hydroxyethyl)-5,6-dihydro-2*H*-pyrans, employing the sequence of the hetero-Diels–Alder, the Luche reduction, and the Ireland–Claisen rearrangement has been presented. The synthetic utility of this strategy was illustrated by the enantioselective synthesis of (–)-centrolobine.

Experimental Section

(*S*)-2-(4-Methoxyphenyl)-2*H*-pyran-4(3*H*)-one 5a. General Procedure for (salen)Cr(III)-Catalyzed Reaction of Aldehydes with Danishefsky's Diene 3. The mixture of catalyst (*S,S*)-**2** (0.06 mmol, 2 mol %), MTBE (0.6 mL), and anisaldehyde (408 mg, 3 mmol) under argon atmosphere was cooled to –10 °C, and Danishefsky diene (0.9 mL, 4.5 mmol) was added dropwise. The cooling bath was removed, and the reaction mixture was stirred for 24 h at rt. After that time, CH₂Cl₂ (3 mL) was added followed by trifluoroacetic acid (ca. 10 drops). After being stirred for 10 min, the reaction mixture was filtered through a pad of Celite, concentrated, and subjected to chromatography (hexane/AcOEt 8:2→7:3). The desired product was dried under vacuum at 40 °C for 3 h, yielding a yellowish solid (557 mg, 2.7 mmol, 91%, 93% ee): mp 50–52 °C (hexane–AcOEt); [α]_D²⁵ = 132.7 (*c* = 1.06, 93% ee, CHCl₃); ¹H NMR 2.63 (ddd, *J* = 16.8, 3.4, 1.3, 1H), 2.92 (dd, *J* = 16.8, 14.4, 1H), 3.82 (s, 3H), 5.37 (dd,

14.4, 3.4, 1H), 5.51 (dd, *J* = 6.0, 1.3, 1H), 6.92–6.96 (m, 2H), 7.31–7.35 (m, 2H), 7.45 (dd, *J* = 6.0, 0.7, 1H); ¹³C NMR 44.1, 55.3, 80.9, 107.2, 114.2, 127.7, 129.8, 160.1, 163.2, 192.3; IR (film) ν 3064, 2983, 2957, 2935, 2905, 2834, 1673, 1613, 1592, 1515, 1270, 1247, 1236, 1229, 1181, 1044, 1031; HRMS (*M* + Na)⁺ calcd for C₁₂H₁₂O₃Na 227.0679, found 227.0673; HPLC (AD-H, *n*-hexane/Pr⁺OH, 9:1, 1 mL/min) *t*_{R(R)} = 13.2, *t*_{R(S)} = 14.4.

(2*S*,4*S*)-2-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-ol 6a. General Procedure for Luche Reduction of 2-Substituted 2*H*-Pyran-4(3*H*)-ones 6. To the solution of CeCl₃·7H₂O (1.04 g, 2.8 mmol) in methanol (5 mL) at –30 °C was added dropwise a solution of ketone **5a** (536 mg, 2.6 mmol) in CH₂Cl₂ (5 mL), followed by addition of NaBH₄ (106 mg, 2.8 mmol). After being stirred for 30 min at –30 °C, the reaction mixture was warmed to rt and NH₄Cl (aq, satd., 5 mL) was added dropwise. The mixture was filtered through a pad of Celite and extracted with CH₂Cl₂ (3 × 20 mL). Combined organic extracts were washed with NH₄Cl (aq, satd., 10 mL), dried with MgSO₄, and concentrated yielding titled compound as a yellowish solid (521 mg, 2.5 mmol, 96%), which was sufficiently pure (by NMR) and was used without further purification: ¹H NMR 1.45 (brs, 1H), 2.00 (ddd, *J* = 13.2, 11.8, 9.3, 1H), 2.35 (ddt, *J* = 13.2, 6.6, 2.0, 1H), 3.81 (s, 3H), 4.59 (brt, *J* = 7.8, 1H), 4.84 (dt, *J* = 6.2, 2.0, 1H), 4.94 (dd, *J* = 11.8, 2.0, 1H), 6.50 (dd, *J* = 6.2, 1.1, 1H), 6.88–6.92 (m, 2H), 7.27–7.31 (m, 2H); ¹³C NMR 39.8, 55.3, 63.6, 76.5, 105.6, 114.0, 127.4, 132.4, 145.4, 159.4; IR (film) ν 3296, 3218, 2962, 2931, 2837, 1642, 1615, 1517, 1255, 1228, 1124, 1031; HRMS (*M* + Na)⁺ calcd for C₁₂H₁₄O₃Na 229.0835, found 229.0824.

(2*S*,4*S*)-2-(4-Methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-yl Acetate 7a. General Procedure for Acetylation of 2-Substituted 3,4-Dihydro-2*H*-pyran-4-ols 7. To the solution of (2*S*,4*S*)-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-ol **6a** (505 mg, 2.45 mmol), triethylamine (485 μ L, 3.7 mmol), and DMAP (49 mg, 0.4 mmol) in CH₂Cl₂ (5 mL) cooled to 0 °C was added dropwise acetic anhydride (350 μ L, 3.7 mmol), and the reaction mixture was warmed to rt and stirred for 4 h. After that time, CH₂Cl₂ (20 mL) and NaHCO₃ (aq, 5%, 20 mL) were added, and the mixture was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic phases were washed with NaHCO₃ (aq, satd, 20 mL) and brine (20 mL), dried with MgSO₄, filtered through a thin pad of silica gel (which was then thoroughly washed with CH₂Cl₂), and concentrated yielding the title acetate as a yellowish oil (595 mg, 2.4 mmol, 98%), which was sufficiently pure (by NMR) and was used without further purification: ¹H NMR 1.92–2.15 (m, 1H), 2.01 (s, 3H), 2.36–2.49 (m, 2H), 3.82 (s, 3H), 4.77–4.84 (m, 1H), 4.96 (dd, *J* = 12.0, 2.0, 1H), 5.51–5.62 (m, 1H), 6.57 (dd, *J* = 6.2, 1.0, 1H), 6.84–6.94 (m, 2H), 7.23–7.32 (m, 2H); ¹³C NMR 21.2, 35.4, 55.3, 66.2, 76.3, 101.3, 113.9, 127.3, 132.0, 146.9, 159.4, 170.8.

***tert*-Butyldimethylsilyl 2-((2*S*,6*S*)-6-(4-Methoxyphenyl)-5,6-dihydro-2*H*-pyran-2-yl)acetate 8a. General Procedure for Ireland–Claisen Rearrangement of 2-Substituted 3,4-Dihydro-2*H*-pyran-4-yl Esters 8.** A solution of (2*S*,4*S*)-2-(4-methoxyphenyl)-3,4-dihydro-2*H*-pyran-4-yl acetate **7a** (574 mg, 2.31 mmol) in THF (8 mL) was added dropwise at –78 °C under argon atmosphere to solution of LiHMDS (2.55 mL, 2.55 mmol, 1.0 M in THF) over 10 min, followed by addition of solution of TBSCl (463 mg, 3.1 mmol) in dry HMPA (1.5 mL). The slightly brown solution was warmed to rt and heated to 70 °C for 2 h. After being cooled to rt, the reaction mixture was diluted with petroleum ether (30 mL), treated with NaHCO₃ (aq, 5%, 20 mL), and extracted with petroleum ether (4 × 15 mL). The combined organic phases were washed with brine (20 mL), dried with MgSO₄, and concentrated yielding the title silyl ester as lightly orange oil (815 mg, 97%) which was sufficiently pure (by NMR) and was used without further purification: ¹H NMR 0.25 (s, 3H), 0.26 (s, 3H), 0.91 (s, 9H), 2.17–2.33 (m, 2H), 2.55 (dd,

(15) Nutaitis, C. F.; Bernardo, J. E. *Synth. Commun.* **1990**, *20*, 487.

$J = 15.2, 6.6, 1\text{H}$) 2.68 (dd, $J = 15.2, 7.3, 1\text{H}$), 3.79 (s, 3H), 4.57 (dd, $J = 10.3, 3.7, 1\text{H}$), 4.68–4.74 (m, 1H), 5.75–5.79 (m, 1H), 5.90–5.95 (m, 1H), 6.83–6.88 (m, 2H), 7.26–7.30 (m, 2H); ^{13}C NMR –4.9, –4.8, 17.6, 25.5, 32.8, 42.4, 55.3, 72.6, 75.3, 113.6, 125.6, 127.0, 129.0, 134.7, 158.9, 171.3; IR (film) ν : 2955, 2931, 2899, 2858, 1719, 1515, 1249, 1174, 827; HRMS ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_{20}\text{H}_{30}\text{O}_4\text{SiNa}$ 385.1806, found 385.1811.

2-((2S,6S)-6-(4-Methoxyphenyl)-5,6-dihydro-2H-pyran-2-yl)-ethanol 1a. General Procedure for Reduction of Silyl Esters. A solution of LiAlH_4 (2.6 mL, 2.6 mmol, 1.0 M in THF) was added dropwise at 0 °C to *tert*-butyldimethylsilyl 2-((2S,6S)-6-(4-methoxyphenyl)-5,6-dihydro-2H-pyran-2-yl)acetate **8a** (815 mg, 2.25 mmol) in THF (10 mL), and the resulting solution was heated to 65 °C for 3 h. After that time, the reaction was cooled to 0 °C, and a solution of sodium–potassium tartrate (aq, satd., 10 mL) was added dropwise. The resulting mixture was warmed to rt, stirred for 10 min, and extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried with MgSO_4 , concentrated, and subjected to column chromatography (hexane/AcOEt 7:3) yielding **1a** as nearly colorless oil (438 mg, 1.87 mmol, 81%): ^1H NMR 1.79–1.86 (m, 1H), 1.90–1.97 (m, 1H), 2.17–2.24 (m, 1H), 2.29–2.38 (m, 1H), 2.55 (brs, 1H), 3.77–3.89 (m, 2H), 3.79 (s, 3H), 4.54–4.61 (m, 2H), 5.66–5.70 (m, 1H), 5.91–5.97 (m, 1H), 6.85–6.89 (m, 2H), 7.24–7.30 (m, 2H); ^{13}C NMR 32.8, 37.2, 55.2, 60.9, 75.8, 76.0, 113.8, 125.4, 127.0, 129.6, 134.5, 159.1; IR (film) ν 3391, 3033, 2954, 2934, 2836, 1644, 1614, 1515, 1247, 1175, 1098, 1058, 1035, 829; HRMS ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_{14}\text{H}_{18}\text{O}_3\text{Na}$ 257.1148, found 257.1141.

(–)-Centrolobine. NaBH_4 (350 mg, 10 mmol) was added to vigorously stirred solution of alcohol **15** (328 mg, 1 mmol) in

THF (10 mL), followed by dropwise addition of trifluoroacetic acid (3 mL) over 30 min. The reaction mixture was stirred for 1 h, carefully neutralized with of NaOH (aq, 5%, ca. 10 mL), and extracted with Et_2O (4 × 15 mL). The combined organic phases were washed with NH_4Cl (aq, satd, 15 mL) and brine (15 mL), dried with MgSO_4 , concentrated, and subjected to column chromatography (hexane/AcOEt 8:2 → 7:3), yielding (–)-centrolobine as white crystals (227 mg, 0.73 mmol, 73%, 93% ee): mp = 87–88 °C (lit.³¹ mp 87–89); $[\alpha]_{\text{D}}^{25} = -86.3$ ($c = 1.02$, 93% ee, CHCl_3) [lit.^{3a} ($[\alpha]_{\text{D}}^{23} = -93.1$, $c = 0.16$, CHCl_3)]; ^1H NMR 1.28–1.37 (m, 1H), 1.46–1.60 (m, 1H), 1.58–1.76 (m, 3H), 1.79–1.95 (m, 3H), 2.61–2.75 (m, 2H), 3.43–3.47 (m, 1H), 3.79 (s, 3H), 4.29 (dd, $J = 11.2, 1.8, 1\text{H}$), 4.80 (brs, 1H), 6.69–6.72 (m, 2H), 6.87–6.89 (m, 2H), 7.01–7.05 (m, 2H), 7.31–7.40 (m, 2H); ^{13}C NMR 24.0, 30.7, 31.2, 33.3, 38.3, 55.3, 77.2, 79.1, 113.6, 115.1, 127.1, 129.5, 134.6, 135.8, 153.5, 158.7; IR (KBr) ν 3391, 2946, 2925, 2913, 2858, 2832, 1611, 1512, 1244; HRMS ($\text{M} + \text{Na}$)⁺ calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3\text{Na}$ 335.1618, found: 335.1633; HPLC (AD-H, *n*-hexane/*Pr*OH, 9:1, 1 mL/min) $t_{\text{R}(-)} = 14.8$, $t_{\text{R}(+)} = 20.0$.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.