Published in final edited form as:
Synthesis (Stuttg). 2008 October 1; 2008(19): 3142–3147. doi:10.1055/s-2008-1067260.

Enantio- and Diastereodivergent Synthetic Route to Multifarious Cyclitols from D-Xylose via Ring-Closing Metathesis

Giovanni Luchetti[a], **Kejia Ding**[b], **Marc d'Alarcao**[*,b], and **Alexander Kornienko**[*,a]

[a]Department of Chemistry, New Mexico Institute of Mining and Technology, Socorro, New Mexico 87801, USA

[b]Department of Chemistry, San José State University, One Washington Square, San José, California 95192, USA

Abstract

Short stereoselective syntheses of various cyclitols, including the derivatives of conduritol B, conduritol F, *myo*-inositol and *chiro*-inositol, have been accomplished. The key steps in the syntheses are a ring-closing metathesis process and a diastereodivergent organometallic addition to a D-xylose-derived alde-hyde.

Keywords

conduritol; inositol; Grignard; stereochemistry model; chelation; Felkin-Anh; cyclophellitol; latent symmetry

The realization that inositols (hexahydroxycyclohexanes), conduritols (tetrahydroxycyclohexenes) and their numerous derivatives play important biological roles has made their study an important endeavor in health-related sciences.[1] Thus, *myo*-inositol phosphates have been intensively investigated for their role in intracellular signal transduction and calcium mobilization.[1d,2] Both *myo*- and *chiro*-inositols have been studied as components of inositolphosphoglycans (IPGs), believed to be important in insulin signaling.[3] It was discovered that various conduritols act as modulators of insulin release[4] and possess antifeedant, antibiotic, anticancer, and growth-regulating activities.[5] Conduritol epoxides, and more prominently fungal metabolite cyclophellitol, are potent glycosidase inhibitors and are under investigation as inhibitors of HIV infection and cancer metastasis.[6]

These and related research activities have generated considerable synthetic effort directed at developing practical preparations of the numerous biologically important cyclitols and their derivatives. Commercially available, inexpensive *myo*-inositol has been a common starting point in the syntheses of *myo*-inositol derivatives,[7] while significantly more expensive naturally occurring methylated *chiro*-inositols, pinitol and quebrachitol, have been utilized to prepare cyclitols with D- and L-*chiro*-inositol stereochemical configurations respectively.[8] However, labor-intensive selective hydroxyl protection/deprotection strategies and the necessity of optical resolution of racemic *myo*-inositol derivatives have led to utilization of chiral pool starting materials for cyclitol syntheses. Of these, carbohydrates represent a logical choice due to their availability in optically pure form and stereochemically complex oxygenation patterns that can be relayed to their target destinations in the desired cyclitols.

*Fax +1(575)8355364; E-mail: akornien@nmt.edu. *Fax +1(408)9244945; E-mail: mdalarcao@science.sjsu.edu.

Thus, D-glucose,[9] D-galactose,[10] D-mannitol,[11] and L-iditol,[12] among others, have served as starting points in efficient syntheses of cyclitol derivatives. One of our research groups has recently reported an enantiodiver-gent synthesis of (+)- and (-)-cyclophellitol from D-xylose.[13] Utilizing the latent plane of symmetry present in the starting carbohydrate, aldehydes **1** and ent-**1** were prepared as key intermediates for this enantiodivergent strategy (Scheme 1). In this paper we show that this chemistry has a much broader scope and provide a full account of an investigation resulting in the development of synthetic pathways to diverse cyclitols starting from D-xylose and utilizing a ring-closing metathesis reaction for carbocycle formation.[14,15]

Transformation of aldehyde **1** to biologically important conduritols and inositols can be achieved using a short synthetic sequence that starts with a Grignard addition of a vinyl metal reagent to generate an inseparable epimeric mixture of alcohols **2** and **3** (Scheme 2). The ratio of the two is highly dependent on the nature of the vinyl metal reagent, solvent and the presence of chelating salts. The highest selectivity for syn alcohol **2** (**2:3** = 4.3:1) is attained using vinylMgBr in CH_2Cl_2 at -78 °C,[16] whereas a preponderance of anti alcohol **3** is observed in the presence of 3 equiv. of $MgBr_2{\cdot}OEt_2$ under the otherwise similar conditions (**2:3** =1:8).

The stereochemical assignment of the syn and anti addition products was confirmed by their conversion to the corresponding tetrabenzyl ethers, whose NMR analysis revealed the symmetry of the syn alcohol-derived compound. Although **2** and **3** can in principle be separated, for example by converting them into corresponding TIPS ethers and then desilylating,[17] direct treatment of their mixture with the first generation Grubbs' ruthenium catalyst gives chromatographically separable conduritols B (**4**) and F (**5**). The facility of the metathesis process is remarkable. TLC monitoring of the reaction progress reveals complete conversion seconds after the catalyst is added to the reaction mixture. The overall yields of the conduritol mixtures from aldehyde **1** are in the range of 85-90%, but the individual yields vary depending on the conditions used to perform the Grignard reaction and they are dependent on the ratio of intermediate alcohols **2** and **3**.

Conduritols **4** and **5** are further benzylated and dihydroxylated to give *myo*- and *chiro*-inostiol derivatives **8** and **9** in good yields. While the C_2-symmetry of **6** accounts for the formation of only one possible cis dihydroxy compound **8**, the facial preference of the dihydroxylation reaction leading to the exclusive formation of **9** is noteworthy. Evidently, the two vicinal benzyloxy substituents flanking the olefin in **7** provide a strong steric bias resulting in the observed stereochemical outcome. The NMR spectra of **8** and **9** are consistent with those previously reported for these compounds by us[18] and others.[19]

We also found that conduritols **4** and **5** are excellent substrates for Mitsunobu inversion. Thus, the yield of a desired conduritol, regardless of whether it is **4** or **5**, can be further improved by treating the minor unwanted epimer with Ph_3P, *p*-nitrobenzoic acid and diisopropylazadicarboxylate in ether to afford *p*-nitrobenzoates **10** and **11**, which are smoothly hydrolyzed to **5** and **4** respectively (Scheme 3).

The diastereodivergence of this synthetic pathway arises from the stereocontrol in the Grignard reaction of aldehyde **1** with vinyl magnesium bromide. Before the conditions favoring the formation of **2** over **3** and vice versa were found, extensive experimentation had been performed and the observed general trends warrant a discussion. Factors controlling the stereochemistry of organometallic addition reactions with α-alkoxy, and even α,β-dialkoxy, aldehydes have been investigated in some detail.[20] However, such processes are considerably more complicated in the case of carbohydrate-derived aldehydes, which may contain additional alkoxy groups capable of chelation.

Generally, researchers have interpreted the stereochemical outcomes of such reactions in terms of Felkin-Anh (Figure 1a, transition state **A**), α-chelation (Figure 1b, transition state **C**), and

β-chelation (Figure 1c, transition state **E**) models.[20a] When applied to aldehyde **1**, these models will be represented by transition states **B, D** and **F**, which will lead to the formation of anti, syn and anti (**3, 2**, and **3**) alcohols, correspondingly.

It appears that the reaction can be channeled through **B, D** or **F** by adjusting the chelating power of the reaction medium.[21] Non-chelating reagents would be expected to react through the Felkin-Anh transition state **B**, leading to the selective formation of anti alcohol **3**. Our results with vinylLi (Table 1, entries 1-4) are consistent with this interpretation and can be explained by the low chelating ability of organolithium reagents in ethereal solvents. Macdonald, Reetz, and more recently Evans and co-workers, have reached similar conclusions in their investigations of Li- and Ti-based organometallic addition reactions to α,β-dialkoxy aldehydes.[20b,22] Literature reports indicate that the selectivity can be switched from anti to syn by replacing organolithium reagents with their organomagnesium counterparts.[20b,23] Due to the higher chelating ability of Mg^{2+} the operative transition state for these addition reactions should be **D** and the results of our experiments with aldehyde **1** (entries 5,6) are consistent with this proposal. The replacement of Lewis basic ethereal solvents with CH_2Cl_2 should further strengthen the metal coordination in transition state **D** and this is also well-precedented in the literature.[22a,24] Indeed complete removal of THF from the commercial vinylMgBr reagent and its substitution by CH_2Cl_2 gives the highest syn selectivity we have been able to attain (entry 9).[16]

Finally, we propose that the syn to anti switch that occurs with increasing amounts of $MgBr_2{\cdot}OEt_2$ (entries 10-12), should be interpreted in terms of the β-chelation controlled transition state **E**. Here, the second metal coordination event with the participation of α- and γ-alkoxyl groups leads to reactive conformer **F**, in which the perpendicular geometry of Cα-OBn bond and coordination of this α-alkoxyl to the metal would enhance the "Anh effect." This hypothesis is in agreement with the results reported by Martin and co-workers, who found that the selectivity of organometallic addition to α,β,γ-trialkoxyaldehyde was crucially dependent on the protecting group on the γ-oxygen.[25] The reaction stereochemistry was completely reversed when the nonchelating γ-TBDPS ether was replaced by the benzyloxy moiety, arguing in favor of an α- to β-chelation switch similar to the one proposed in this work.

Although we found that the highest selectivities favoring both syn and anti alcohols **2** and **3** are obtained in CH_2Cl_2, the practicality of these procedures, especially performed on a large scale, are somewhat undermined by the side-reaction of the Grignard reagent with the solvent and, therefore, the necessity to use a large excess of the reagent (20 equiv.). The procedures involving the use of vinylLi in ether (**2:3** = 1:3.5) and vinylMgBr in CH_2Cl_2-THF 5:1 (**2:3** = 3:1) may be recommended for large-scale preparations.

In conclusion, a short synthetic route to a diverse group of cyclitol derivatives has been developed. The synthesis is enantiodivergent and allows for the preparation of various derivatives of conduritols B and F as well as *myo*- an *chiro*-inositols in both enantiomeric series. In addition, conduritol B derivative ent-**4** served as a penultimate intermediate in the synthesis of (+)-cyclophellitol by Trost and co-workers.[26] Therefore, our route provides another strategy for an enantiodivergent synthesis of this intensively researched anti-HIV and antimetastic agent and, more importantly, a library of its analogues in both enantiomeric series. Finally, we believe that our studies of the stereochemical outcome of the vinyl metal addition to a carbohydrate-derived aldehyde shed more light on these generally poorly understood processes.

Unless otherwise noted all commercially obtained reagents were used without purification. THF was distilled from sodium benzophenone ketyl prior to use. Dichloromethane was distilled from calcium chloride. Reactions were carried out under a nitrogen atmosphere in oven-dried

glassware using standard syringe, cannula and septa techniques. Reactions were monitored by TLC (Silica Gel 60 F_{254}, 250 μm) and visualized with UV light and ceric ammonium molybdate solution. Flash chromatography was performed on silica gel (32-63 μm). Optical rotations were measured with an Autopol III automatic polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on JEOL 300 MHz spectrometer.

3(S),4(R),5(R)-Tribenzyloxy-6(S)-hydroxycyclohexene (4)

To a 1M solution of vinylmagnesium bromide in CH_2Cl_2 (23 mL) was added aldehyde **1** (0.5 g, 1.2 mmol) in CH_2Cl_2 (7 mL) dropwise during 30 min at -78 °C. The mixture was stirred at that temperature for 3 h and MeOH (2 mL) was added to quench the excess of the Grignard reagent. The mixture was warmed up to rt and washed with H_2O (10 mL), aqueous 1M NH_4Cl (10 mL), H_2O (10 mL) and brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The residue consisted of a 4.3:1 (based on the integration of doublets at 2.64 and 3.25 ppm) mixture of **2** and **3**, which was chromatographed (hexanes - ethyl acetate, 6:1). To a solution of **2** and **3** (0.46 g, 4.3:1) in CH_2Cl_2 (40 mL) was added $(Cy_3P)_2RuCl_2(CHPh)$ (56 mg, 0.068 mmol) at rt. The reaction mixture was stirred for 15 min and opened to the atmosphere for 4 h. The solvent was evaporated and the residue chromatographed (hexanes - ether, 1:1 → 1:2) to give 0.35 g (70%) of **4**, followed by 80 mg (16%) of **5**.

$[\alpha]_D^{20}$: +123.3 (c 0.8, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.25-7.36 (m, 15H), 5.70 (m, 2H), 5.03 (d, *J* = 11.3 Hz, 1H), 4.92-4.25 (m, 5H), 4.32-4.25 (m, 2H), 3.79 (dd, *J* = 7.4, 10.2 Hz, 1H), 3.53 (dd, *J* = 8.0, 10.1 Hz, 1H), 2.22 (d, *J* = 3.9 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ = 138.7, 138.3, 129.5, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.8, 127.1, 84.4, 83.4, 80.6, 75.4, 72.4, 72.0.

HRMS (ESI): *m/z* calcd for $C_{27}H_{28}NaO_4$ $(M+Na)^+$ 439.1885; found: 439.1884.

3(S),4(R),5(R)-Tribenzyloxy-6(R)-hydroxycyclohexene (5)

To a solution of aldehyde **1** (0.5 g, 1.2 mmol) in CH_2Cl_2 (11 mL) was added magnesium bromide etherate (0.92 g, 3.6 mmol) in one portion and the mixture was stirred at rt for 30 min. To a cold (-78 °C) mixture was added vinylmagnesium bromide in CH_2Cl_2 (24 mL of 1M solution, 24 mmol) over a period of 30 min. The reaction mixture was stirred at -78 °C for 3 h after which time methanol (10 mL) was added. The mixture was allowed to warm up to rt and treated with 1M NH_4Cl (25 mL). The aqueous layer was extracted with additional CH_2Cl_2 (2 × 25 mL) and the combined organic extracts were washed with water (40 mL), brine (40 mL) and dried ($MgSO_4$). The residue consisted of a 1:8.5 (based on the integration of doublets at 2.61 and 3.15 ppm) mixture of **2** and **3**, which was chromatographed (hexanes - ethyl acetate, 6:1). To a solution of **2** and **3** (0.44 g, 1:8.5) in CH_2Cl_2 (40 mL) was added $(Cy_3P)_2RuCl_2(CHPh)$ (56 mg, 0.068 mmol) at rt. The reaction mixture was stirred for 15 min and opened to the atmosphere for 4 h. The solvent was evaporated and the residue chromatographed (hexanes - ether, 1:1 → 1:2) to give 0.39 g (79%) of **5**, preceded by 50 mg (10%) of **4**.

$[\alpha]_D^{20}$: +39.3 (c 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 7.35-7.25 (m, 15H), 5.88 (d, *J* = 1.9 Hz, 2H), 4.94-4.66 (m, 6H), 4.29 (m, 1H), 4.10 (d, *J* = 7.4 Hz, 1H), 4.50 (dd, *J* = 7.2, 9.7 Hz, 1H), 3.56 (dd, *J* = 4.1, 9.7 Hz, 1H), 2.71 (d, *J* = 2.5 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ = 138.8, 138.6, 138.2, 131.0, 128.6, 128.5, 128.1, 128.0, 127.8, 127.7, 127.0, 79.7, 79.1, 79.0, 75.2, 73.2, 72.0, 65.7.

HRMS (ESI): *m/z* calcd for $C_{27}H_{28}NaO_4$ $(M+Na)^+$ 439.1885; found: 439.1885.

3(S),4(R),5(R),6(S)-Tetrabenzyloxycyclohexene (6)[19]

To a solution of **4** (7 mg, 0.017 mmol) in DMF (0.6 mL) was added NaH (4 mg of 60% dispersion in mineral oil, 0.1 mmol) at 0 °C. The mixture was stirred for 15 min after which time BnBr (5 μL, 0.04 mmol) was added and the resulting solution was stirred overnight. Ether (3 mL) was added and the excess of NaH was quenched with 1M NH_4Cl (2 mL). The organic layer was washed with water (2 × 2 mL), dried ($MgSO_4$) and evaporated. The residue was subjected to a preparative chromatography plate (hexanes - ethyl acetate, 9:1) to give 7.5 mg (88%) of **6**, whose ^{1}H NMR spectrum was identical to that reported previously.[19]

3(S),4(R),5(R),6(R)-Tetrabenzyloxycyclohexene (7)[27]

To a solution of **5** (8 mg, 0.019 mmol) in DMF (0.6 mL) was added NaH (4 mg of 60% dispersion in mineral oil, 0.1 mmol) at 0 °C. The mixture was stirred for 15 min after which time BnBr (5 μL, 0.04 mmol) was added and the resulting solution was stirred overnight. Ether (3 mL) was added and the excess of NaH was quenched with 1M NH_4Cl (2 mL). The organic layer was washed with water (2 × 2mL), dried ($MgSO_4$) and evaporated. The residue was subjected to a preparative chromatography plate (hexanes - ethyl acetate, 9:1) to give 9 mg (94%) of **7**, whose ^{1}H NMR spectrum was identical to that reported previously.[27]

3,4,5,6-Tetra-*O*-benzyl-D-*myo*-inositol (8)[19]

To a solution of **6** (6 mg, 0.012 mmol) and NMO (2 mg, 0.017 mmol) in acetone-H_2O (9:1, 0.6 mL) was added a catalytic amount of OsO_4. The mixture was stirred for 3 days at rt and treated with ether (3 mL). The organic layer was washed with 10% $Na_2S_2O_3$ (2mL), H_2O (2 mL), dried ($MgSO_4$) and evaporated. The residue consisted of **8**, which was >98% pure by TLC and ^{1}H NMR (5.8 mg, 89%). ^{1}H NMR spectrum of **8** was identical to that reported previously.[19]

1,2,3,4-Tetra-*O*-benzyl-L-*chiro*-inositol (9)[18]

To a solution of **7** (6 mg, 0.012 mmol) and NMO (2 mg, 0.017 mmol) in acetone-H_2O (9:1, 0.6 mL) was added a catalytic amount of OsO_4. The mixture was stirred for 2 h at rt and treated with ether (3 mL). The organic layer was washed with 10% $Na_2S_2O_3$ (2mL), H_2O (2 mL), dried ($MgSO_4$) and evaporated. The residue consisted of **9**, which was >98% pure by TLC and ^{1}H NMR (5.9 mg, 93%). ^{1}H NMR spectrum of **9** was identical to that reported previously.[18]

Mitsunobu Inversion of Conduritols 4 and 5

To a stirred solution of **4** or **5** (30 mg, 0.072 mmol) in ether (1.25 mL) was added PPh_3 (19 mg, 0.072 mmol) and *p*-nitrobenzoic acid (12 mg, 0.072 mmol) at rt. After the material dissolved, DIAD (17.7 μL, 0.074 mmol) was added to the reaction mixture. After stirring for 17 h at rt, the mixture was concentrated under reduced pressure and the residue was chromatographed (hexanes - ethyl acetate, 9:1) to yield pure **10** (37 mg, 89%) or **11** (39 mg, 94%).

(1R,4S,5R,6R)-4,5,6-Tris(benzyloxy)cyclohex-2-enyl 4-nitrobenzoate (10)

$[\alpha]_D^{20}$: -114.3 (c 0.1, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 8.28 (d, *J* = 8.5 Hz, 2H), 8.18 (d, *J* = 8.5, 2H), 7.36-7.23 (m, 15H), 6.04-5.87 (m, 3H), 4.99-4.67 (m, 6H), 4.16-4.04 (m, 2H), 3.73 (dd, *J* = 3.0, 9.9 Hz, 1H).

^{13}C NMR ($CDCl_3$): δ = 164.3, 150.6, 138.6, 138.2, 138.0, 135.7, 134.2. 131.0, 128.8, 128.6, 128.4, 128.2, 128.0, 127.8, 123.6, 123.1, 79.8, 78.4, 77.9, 77.3, 75.3, 72.8, 68.3.

HRMS (ESI): *m/z* calcd for $C_{34}H_{31}NNaO_7$ $(M+Na)^+$ 588.1998; found: 588.1982.

(1S,4S,5R,6R)-4,5,6-Tris(benzyloxy)cyclohex-2-enyl 4-nitrobenzoate (11)

$[\alpha]_D^{20}$: +156.8 (c 0.05, $CHCl_3$).

^{1}H NMR ($CDCl_3$): δ = 8.24 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.36-7.10 (m, 15H), 5.83 (m, 2H), 5.64 (d, *J* = 10.5 Hz, 1H), 4.98-4.67 (m, 6H), 4.30 (dd, *J* = 2.8, 4.7 Hz, 1H), 3.93-3.85 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 164.1, 150.6, 138.5, 138.1, 135.3, 130.9, 130.0, 128.6, 128.5, 128.4, 128.1, 128.1, 127.9, 127.7, 125.4, 123.5, 83.8, 81.1, 79.8, 77.5, 75.8, 75.7, 72.7.

HRMS (ESI): *m/z* calcd for $C_{34}H_{31}NNaO_7$ $(M+Na)^+$ 588.1998; found: 588.1995.

Hydrolysis of Esters 10 and 11

To a stirred solution of **10** or **11** (20 mg, 0.035 mmol) in THF (0.5 mL) was added 1M LiOH (0.5 mL). The reaction mixture was stirred for 3 h at rt. The solvent was evaporated and the residue chromatographed (hexanes - ethyl acetate, 9:1) to yield pure **5** (14.1 mg, 97%) or **4** (13.8 mg, 95%).

Acknowledgment

A. K. would like to acknowledge the financial support from the US National Institutes of Health (RR-16480 and CA-99957) under the BRIN/INBRE and AREA programs. M. D. acknowledges the financial support from the National Institutes of Health (DK-44589 and GM-84819). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Dedicated to Professor E. J. Corey on the occasion of his 80th birthday.

References

(1). Posternak, T. Chemistry of the Cyclitols - The Cyclitols. Hermann; Paris: 1965. Hudlicky, T.; Cebulak, M. Cyclitols and Derivatives. A Handbook of Physical, Spectral and Synthetic Data. VCH; New York: 1993. (c) Ferrier RJ, Middleton S. Chem. Rev 1993;93:2779.Billington, DC. The Inositol Phosphates - Chemical Synthesis and Biological Significance. VCH; Weinheim: 1993. (e) Hudlicky T, Entwistle DA, Pitzer KK, Thorpe AJ. Chem. Rev 1996;96:1195. [PubMed: 11848785] (f) Gültekin MS, Çelik M, Balci M. Curr. Org. Chem 2004;8:1159.

(2). Potter BVL, Lampe D. Angew. Chem. Int. Ed. Engl 1995;34:1933.

(3). See: Chakraborty N, d'Alarcao M. Bioorg. Med. Chem 2005;13:6732. and references cited therein. [PubMed: 16115771]

(4). Billington DC, Perron-Sierra F, Beaubras S, Duhault J, Espinal J, Challal S. Bioorg. Med. Chem. Lett 1994;4:2307.

(5). (a) Balci M, Sütbeyaz Y, Seçen H. Tetrahedron 1990;46:3715. (b) Balci M. Pure Appl. Chem 1997;69:97.and references cited therein

(6). (a) Legler G, Herrchen M. FEBS Lett 1981;135:139. [PubMed: 6274683] (b) Atsumi S, Iinuma H, Nosaka C, Umezawa K. J. Antibiot 1990;43:1579. [PubMed: 2148935] (c) Atsumi S, Umezawa K, Iinuma H, Naganawa H, Nakamura H, Iitaka I, Takeuchi T. J. Antibiot 1990;43:49. [PubMed: 2106502]

(7). Sureshan KM, Shashidhar MS, Praveen T, Das T. Chem. Rev 2003;103:4477. [PubMed: 14611268]

(8). Kiddle JJ. Chem. Rev 1995;95:2189.

(9). See, for example: Saito S, Shimazawa R, Shirai R. Chem. Pharm. Bull 2004;52:727. [PubMed: 15187396]

(10). See, for example: Dubreuil D, Cleophax J, de Almeida MV, Verre-Sebrié C, Liaigre J, Vass G, Géro SD. Tetrahedron 1997;53:16747.

(11). See, for example: Chiara JL, Martín-Lomas M. Tetrahedron Lett 1994;35:2969.

(12). See, for example: Guidot JP, Le Gall T, Mioskowski C. Tetrahedron Lett 1994;35:6671.

(13). Kireev AS, Breithaupt AT, Collins W, Nadein ON, Kornienko A. J. Org. Chem 2005;70:742. [PubMed: 15651835]

(14). For preliminary account of this work, see: Kornienko A, d'Alarcao M. Tetrahedron: Asymmetry 1999;10:827.

(15). For other examples of utilization of ring-closing metathesis in cyclitol synthesis, see: (a)Verhelst SHL, Wennekes T, van der Marel GA, Overkleeft HS, van Boeckel CAA, van Boom JH. Tetrahedron 2004;60:2813. (b)Andersen TL, Skytte DM, Madsen R. Org. Biomol. Chem 2004;2:2951. [PubMed: 15480460] (c)Heo JN, Holson EB, Roush WR. Org. Lett 2003;5:1697. [PubMed: 12735755](d)Marco-Contelles J, de Opazo E. J. Org. Chem 2002;67:3705. [PubMed: 12027684] (e)Conrad RM, Grogan MJ, Bertozzi CR. Org. Lett 2002;4:1359. [PubMed: 11950362] (f)Boyer F-D, Hanna I, Nolan SP. J. Org. Chem 2001;66:4094. [PubMed: 11375046] (g)Jorgensen M, Iversen EH, Paulsen AL, Madsen R. J. Org. Chem 2001;66:4630. [PubMed: 11421784] (h) Nishikawa A, Saito S, Hashimoto Y, Koga K, Shirai R. Tetrahedron Lett 2001;42:9195. (i)Hanna I, Ricard L. Org. Lett 2000;2:2651. [PubMed: 10990419] (j)Marco-Contelles J, de Opazo E. J. Org. Chem 2000;65:5416. [PubMed: 10993375] (k)Marco-Contelles J, de Opazo E. Tetrahedron Lett 2000;41:2439. (l)Kapferer P, Sarabia F, Vasella A. Helv. Chim. Acta 1999;82:645. (m)Sellier O, Van de Weghe P, Eustache J. Tetrahedron Lett 1999;40:5859. (n)Seepersaud M, Al-Abed Y. Org. Lett 1999;1:1463.

(16). After our original disclosure of these results (ref. 14), Madsen and co-workers reported that performing this reaction with vinyl magnesium chloride in toluene leads to a higher (5:1) syn selectivity (ref. 15b).

(17). See the next article in this issue.

(18). Kornienko A, Marnera G, d'Alarcao M. Carbohydr. Res 1998;310:141. [PubMed: 9794077]

(19). Yamauchi N, Kakinuma K. J. Antibiot 1992;45:756. [PubMed: 1624377]

(20). (a) Reetz MT. Angew. Chem. Int. Ed. Engl 1984;23:556. (b) Mead K, Macdonald TL. J. Org. Chem 1985;50:422.

(21). Both the organometallic reagent and the reaction solvent are important since Lewis basic solvents such as THF or ether can diminish chelation by strongly coordinating to the metal species.

(22). (a) Reetz MT, Kesseler K. J. Org. Chem 1985;50:5436. (b) Evans DA, Cee VJ, Siska SJ. J. Am. Chem. Soc 2006;128:9433. [PubMed: 16848480]

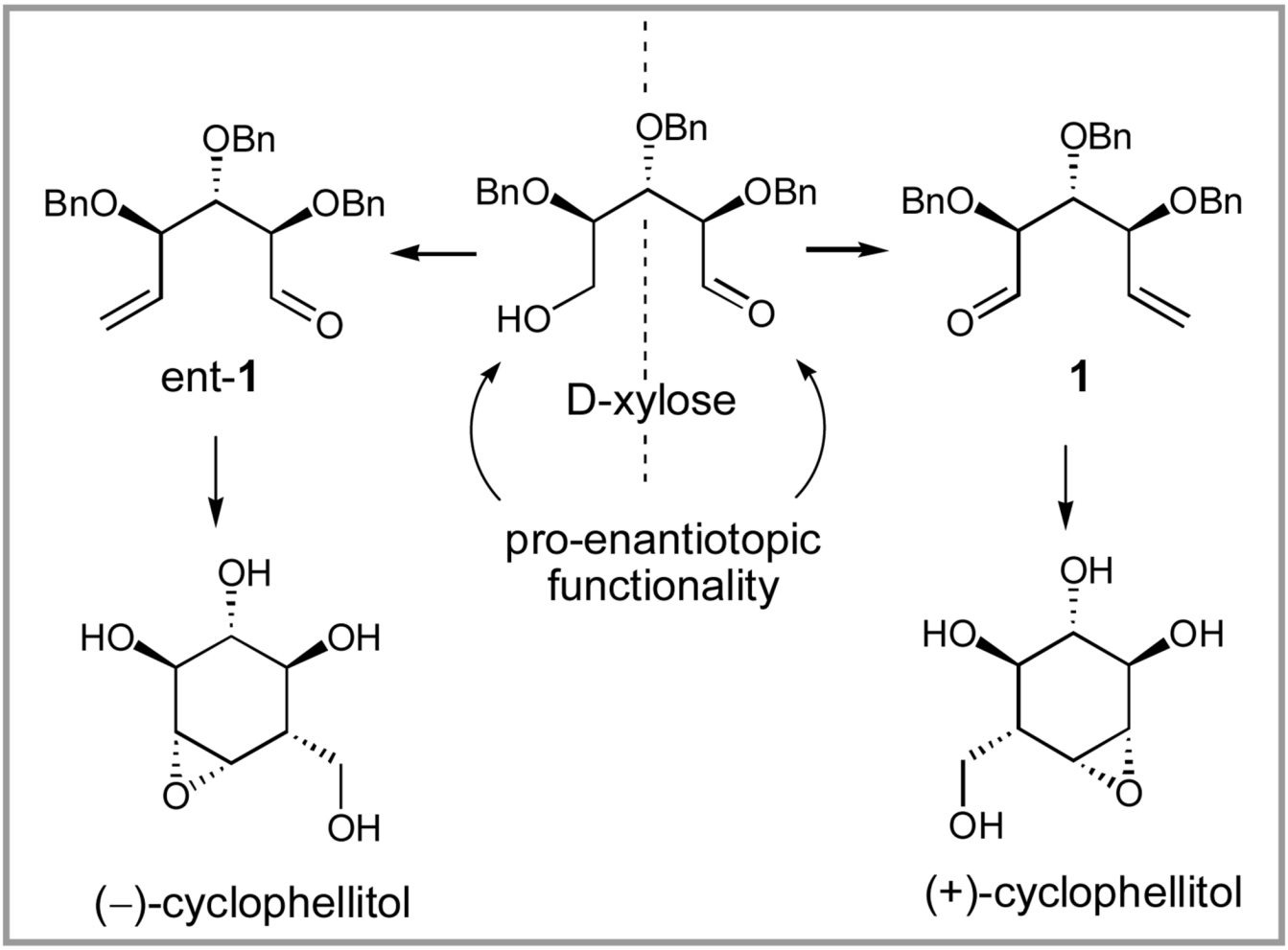
(23). Mead KT. Tetrahedron Lett 1987;28:1019.

(24). (a) Keck GE, Andrus MB, Romer DR. J. Org. Chem 1991;56:417. (b) Guillarme S, Haudrechy A. Tetrahedron Lett 2005;46:3175.

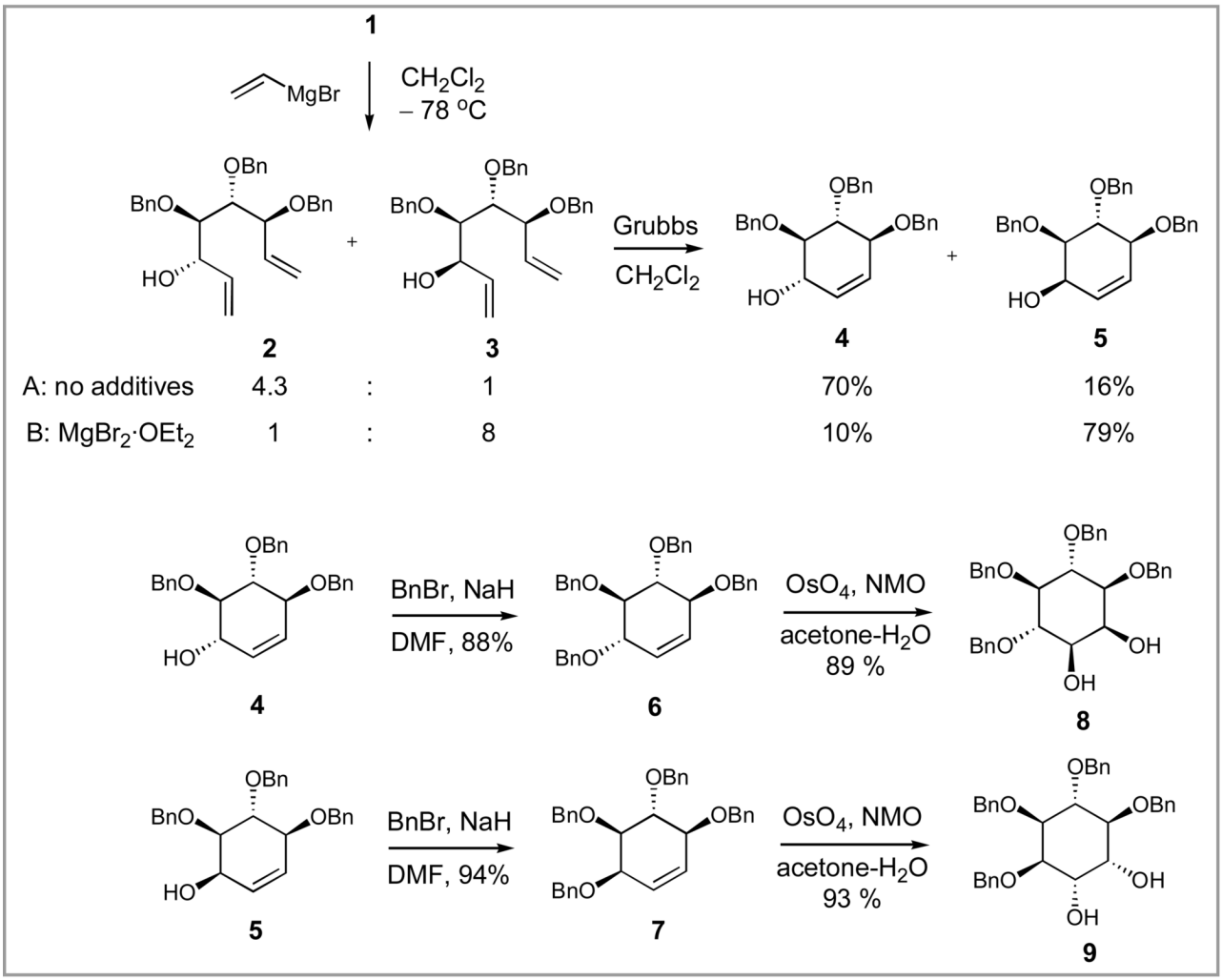
(25). Martin SF, Chen H-J, Yang C-Y. J. Org. Chem 1993;58:2867.

(26). Trost BM, Hembre EJ. Tetrahedron Lett 1999;40:219.

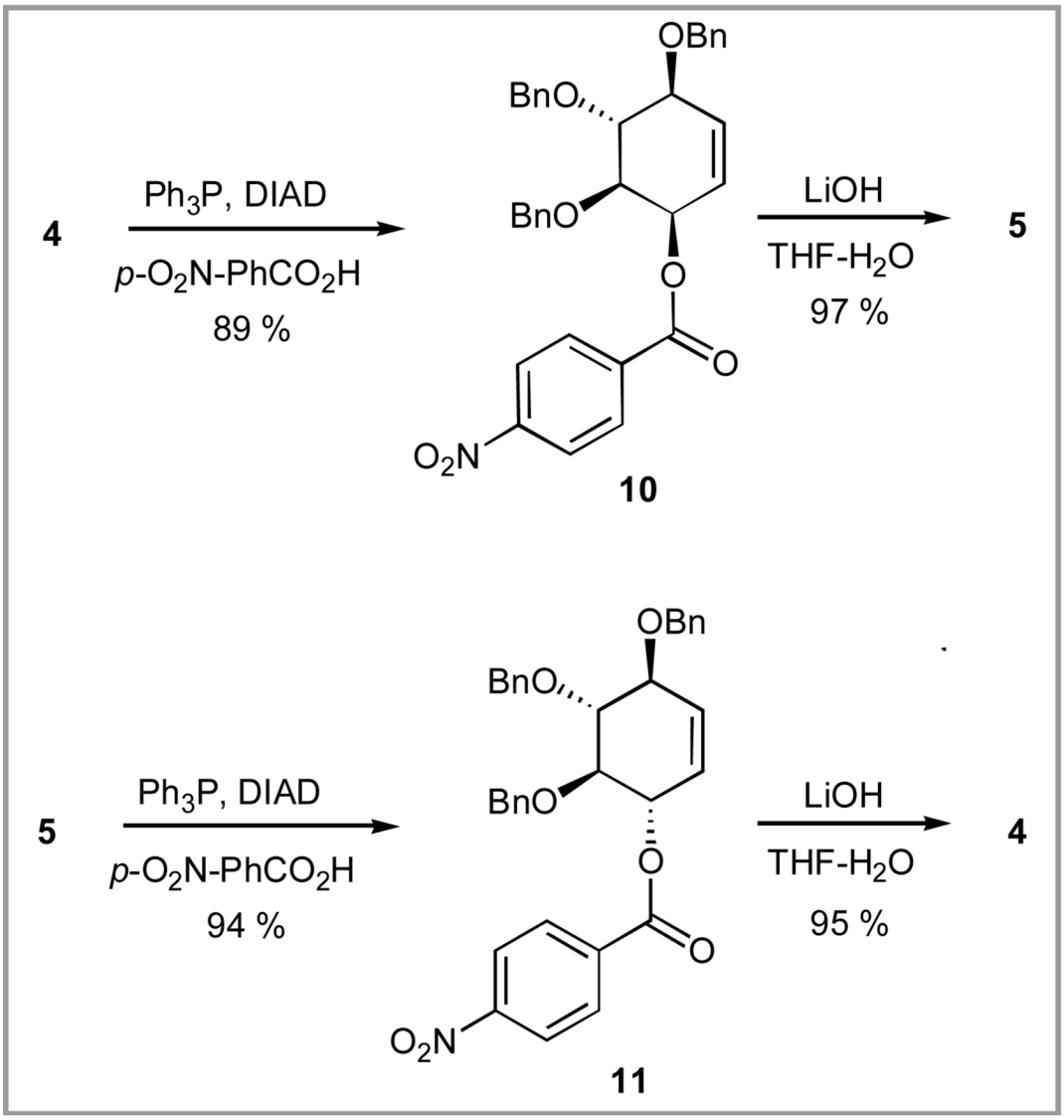
(27). Ackermann L, Tom DE, Fürstner A. Tetrahedron 2000;56:2195.



Scheme 1.
Enantiodivergent strategy utilized in the synthesis of (+)-and (-)-cyclophellitol from D-xylose



Scheme 2.
Syntheses of benzylated derivatives of conduritol B, conduritol F, *myo*-inositol and *chiro*-inositol



Scheme 3.
Mitsunobu inversion interconverting conduritols **4** and **5**

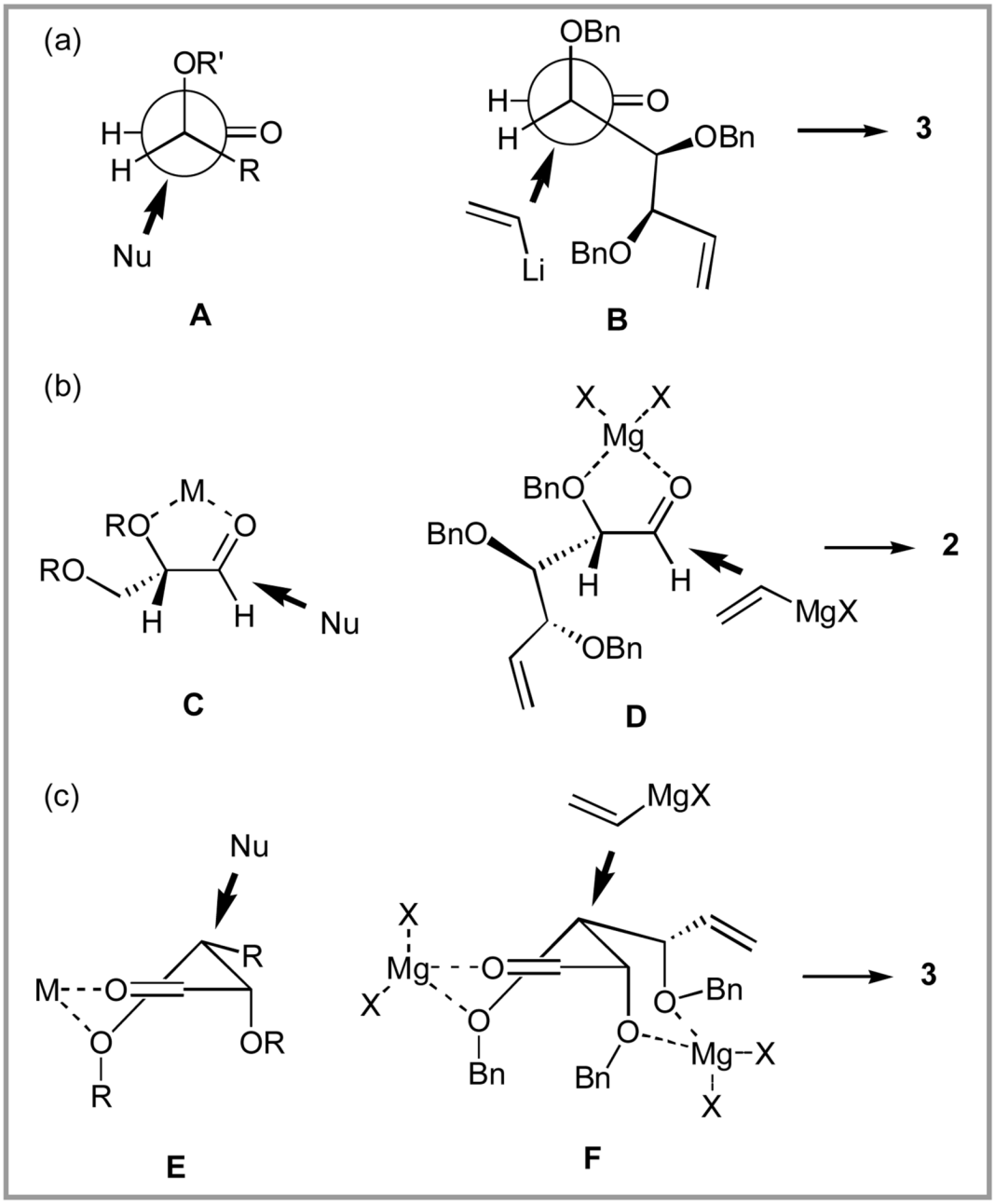


Figure 1.
Possible transition states governing the stereocontrol in vinyl metal addition to aldehyde **1**

Table 1

Stereoselectivities of vinyl metal addition to aldehyde 1

	vinyl metal reagent	solvent	additive	chelation	anti:syn 3:2
1	vinylLi	THF	12-crown-4	low	1.5:1
2	vinylLi	THF	none	low	2.2:1
3	vinylLi	THF	Me_2S	low	2.6:1
4	vinylLi	ether	none	low	3.5:1
5	vinylMgBr	THF-ether 1:1	none	medium	1:2
6	vinylMgBr	THF	none	medium	1:2
7	vinylMgBr	CH_2Cl_2-THF 1:1	none	medium	1:2
8	vinylMgBr	CH_2Cl_2-THF 5:1	none	medium	1:3
9	vinylMgBr	CH_2Cl_2	none	medium	1:4.3
10	vinylMgBr	CH_2Cl_2	$MgBr_2$·OEt2 1 equiv.	high	1:1
11	vinylMgBr	CH_2Cl_2	$MgBr_2$·OEt2 2 equiv.	high	2:1
12	vinylMgBr	CH_2Cl_2	$MgBr_2$·OEt_2 3 equiv.	high	8:1