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Synthesis of the C1–C21 (C1′-C21′) Fragment of the Dimeric Polyketide Natural Product SCH 351448

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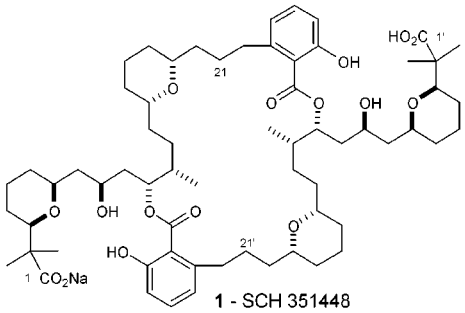
ABSTRACT



1 - SCH 351448

A convergent, stereoselective assembly of the C1–C21 (C1′–C21′) fragment of SCH 351448, a 28-membered bis-lactone natural product, has been developed. A highly efficient approach to this fragment assembles 75% of the carbon skeleton and all the stereochemical elements present in the natural product. In addition, an interesting boron ligand effect on the diastereoselectivity of a key aldol reaction with methyl ketone-derived enolborinates is reported.

Recently, a team working at the Schering-Plough Research Institute disclosed the structure of an intriguing microbial metabolite from *Micromonospora* sp., named SCH 351448 (**1**).[1] The isolation of **1** was guided by its unique ability to specifically activate transcription of a reporter construct under control of the low-density lipoprotein (LDL) receptor promoter. Clearing serum cholesterol levels through increased uptake of LDL by the LDL receptor is important for the prevention and treatment of coronary heart disease.[2] Besides their potential as therapeutic leads, small molecules that uncouple LDL receptor transcription from regulatory feedback mechanisms are potentially valuable tools to study the proteolytic processing of the sterol regulatory element-binding proteins (SREBPs), which are the membrane-bound transcription factors that control activation of the LDL receptor gene.[3]

The structure and relative stereochemistry of SCH 351448 (**1**) was unambiguously established via single-crystal X-ray analysis.[4] SCH 351448 is a unique manifestation of the rich polyketide-producing biosynthetic machinery expressed in microorganisms. Composed of two identical diacids, this 28-membered C_2-symmetric macrocyclic metabolite integrates two salicylic acid moieties and four tetrahydropyranyl rings into a bis-lactone template featuring 14 stereocenters and two quaternary centers. Our synthetic approach is shown in Figure 1 and will exploit the dimeric nature of **1**. Dimerization/cyclization is envisioned to proceed through a sequential esterification/lactonization, a tandem intermolecular/intramolecular olefin metathesis, or a sequential esterification/ring-closing olefin metathesis. Each of the required monomers ultimately will derive from a common precursor, C1−C21 (C1′−C21′) fragment **2** in turn accessible from two tetrahy-

(1) Hegde, V. R.; Puar, M. S.; Dai, P.; Patel, M.; Gullo, V. P.; Das, P. R.; Bond, R. W.; McPhail, A. T. *Tetrahedron Lett.* **2000**, *41*, 1351−1354.

(2) Brown, M. S.; Goldstein, J. L. *Science* **1986**, *232*, 34−47.

(3) Brown, M. S.; Goldstein, J. L. *Cell* **1997**, *89*, 331−340.

(4) The absolute stereochemistry of SCH 351448 has not been assigned.

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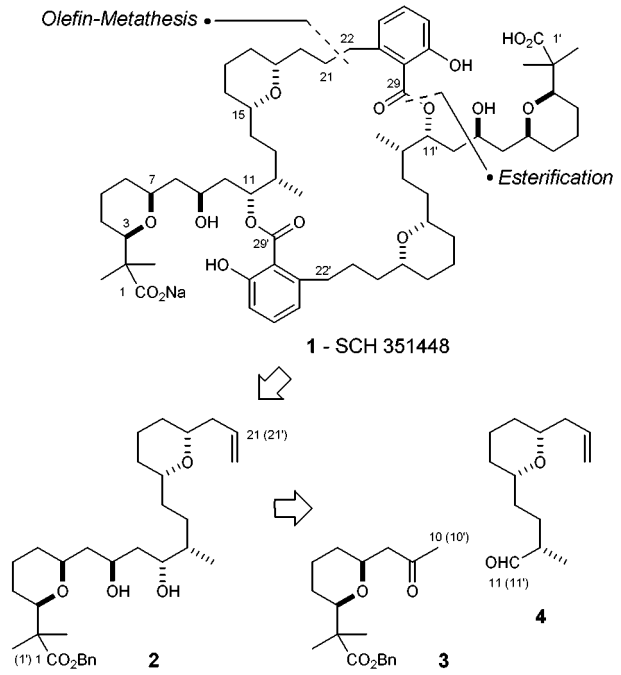
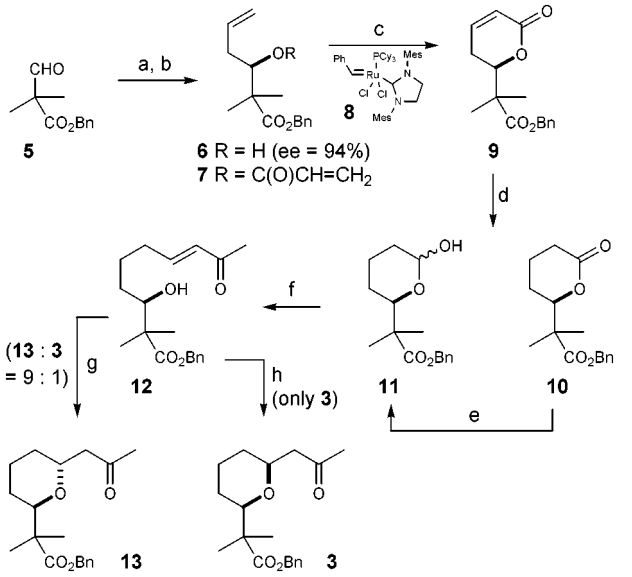


Figure 1. Synthetic strategy for the synthesis of SCH 351448.

dropyranyl fragments **3** and **4** via an aldol reaction. Herein, we report a highly efficient synthesis of fragment **2**, which constitutes 75% of the carbon skeleton and all the stereochemical elements present in the natural product.

A short, seven-step synthesis of fragment **3** is delineated in Scheme 1. Asymmetric allylation[5] of known aldehyde **5**[6] provided homoallyl alcohol **6** (94% ee via Mosher ester analysis),[7] which was further transformed into the acryloate derivative **7** (CH_2═$CHCOCl$, *i*-Pr_2EtN, CH_2Cl_2). Subsequent intramolecular olefin metathesis was best performed with Grubbs' imidazolidinyl ruthenium carbene **8** (5 mol %).[8] A variety of conditions were explored for converting α,β-unsaturated lactone **9** into the saturated lactol **11**. A reducing mixture composed of $CoCl_2$ and $NaBH_4$ in THF provided the desired lactol **11** in one operation but was not reproducible on a larger scale. Instead, a two-step procedure was followed whereby the conjugated double bond was first saturated with $NiCl_2/NaBH_4$ in THF[9] (80%, 7% of lactol **11** was also present) followed by reduction of lactone **10** to lactol **11** with DIBAL-H (96%). Homologation of **11** with 1-triphenylphosphoranyliden-2-propanone proceeded uneventful and set the stage for a base-catalyzed cyclization of enone **12**. As expected, treatment of δ-hydroxy enone **12** with a catalytic amount of *t*-BuOK under equilibrating

Scheme 1[a]



[a] Reagents and conditions: (a) (+)-Ipc_2BOMe, allylMgBr, −78 °C, Et_2O (80%, 94% ee); (b) CH_2═$CHCOCl$, *i*-Pr_2NEt, DMAP, CH_2Cl_2 (83%); (c) 5 mol % **8**, CH_2Cl_2, 4 h, rt (76%); (d) $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF, 0 °C, 2 h (80% **10** + 7% **11**); (e) DIBAL-H, CH_2Cl_2, −78 °C, 1 h (96%); (f) 1-triphenylphosphoranylidene-2-propanone, MeCN, 90 °C, 24 h (70%); (g) *t*-BuOK, THF, −78 °C, 20 min (86%, **13**:**3** = 9:1); (h) *t*-BuOK, THF, 0 °C, 5−10 min (90%, only **3**).

conditions (THF, 0 °C) provided the thermodynamic tetrahydropyranyl ring **3**.[10] Equilibration did not occur at −78 °C (otherwise similar conditions), and a separable (flash chromatography) 9:1 mixture of *trans*- and *cis*-tetrahydropyrans **13** and **3** was obtained.[11] When subjected to *t*-BuOK in THF at 0 °C, purified *trans*-isomer **13** was converted to *cis*-isomer **3** within 10 min (91%).[12]

The synthesis of the C11−C21 (C11′−C21′) fragment **4** commenced with the addition of known methyl 7-oxo-2-heptenoate **14**[13] to a −78 °C solution of *B*-allylbis-(4-isocaranyl)borane[5] to provide homoallyl alcohol **15** (92% ee via Mosher ester analysis, Scheme 2).[7] Unlike the smooth ring-closure of compound **12**, treatment of **15** with *t*-BuOK at 0 °C resulted in a complex mixture of intractable products. Lowering the temperature did provide for a cleaner trans-

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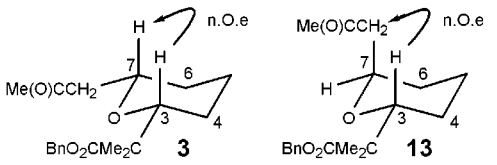
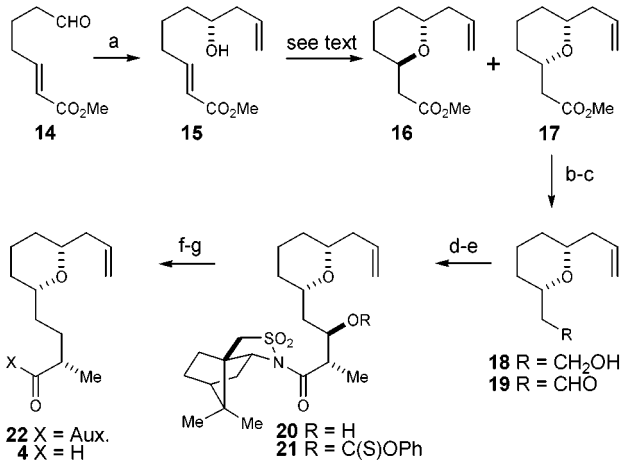
(6) Kim, H.-O.; Carroll, B.; Lee, M. S. *Synth. Commun.* **1997**, *27*, 2505−2515.
(7) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143-2147.
(8) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783−3784.
(9) Satoh, T.; Nanba, K.; Suzuki, S. *Chem. Pharm. Bull.* **1971**, *19*, 817−820.

(10) Evans, D. A.; Carreira, E. M. *Tetrahedron Lett.* **1990**, *31*, 4703−4706.
(11) The stereochemistry was assigned on the basis of ^1H NMR coupling constants and NOE experiments (**3**, $^3J_{H3-H4e}$ = 1.6 Hz, $^3J_{H3-H4a}$ = 11.2 Hz, $^3J_{H7-H6e}$ = 1.6 Hz, $^3J_{H7-H6a}$ = 10.8 Hz; **13**, $^3J_{H3-H4e}$ = 1.6 Hz, $^3J_{H3-H4a}$ = 11.2 Hz, $^3J_{H7-H6e}$ = 0 Hz, $^3J_{H7-H6a}$ = 5.2 Hz).



(12) Evans, D. A.; Ripin, D. H. B.; Halstead, D. P.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 6816−6826.
(13) Denmark, S. E.; Middleton, D. S. *J. Org. Chem.* **1998**, *63*, 1604−1618.

Scheme 2[a]

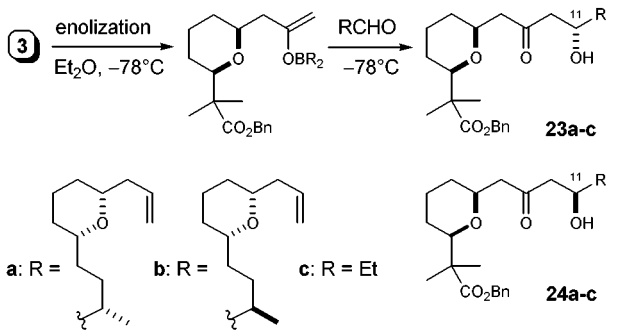


[a] Reagents and conditions: (a) *B*-allyl bis(4-isocaranyl)borane, Et_2O, −78 °C, (70%, 92% ee); (b) $LiAlH_4$, Et_2O, 0 °C (99%); (c) PCC, CH_2Cl_2, 3 h, RT (70%); (d) (2*S*)-*N*-propionyl bornanesultam, $TiCl_4$, *i*-Pr_2NEt, −78 °C; then add **19**, −78 °C (71%); (e) PhOC(S)Cl, py, CH_2Cl_2, 14 h, RT (81%); (f) Bu_3SnH, 10% AIBN, PhH, 7 h, reflux (87%); (g) DIBAL-H, CH_2Cl_2, −78 °C, 1 h; then MeOH, −78 °C, 10 min (70%); or $LiAlH_4$, Et_2O (97%); then Dess-Martin periodinane, CH_2Cl_2 (87%).

formation, and the *cis*-isomer **17** was the only product isolated (80%) after cyclization of **15** at −35 °C (0.6 equiv of *t*-BuOK, THF).[14,15] A reduction/oxidation sequence gave aldehyde **19** which was treated with the *Z*(*O*)-titanium enolate derived from (2*S*)-*N*-propionyl bornanesultam (−78 °C) to deliver the single (by ^{1}H NMR analysis) *β*-hydroxy amide diastereomer **20**.[16] A modified Barton−McCombie deoxygenation[17] via the corresponding phenyl thionocarbonate **21** was followed by a one-step reductive transformation of *N*-acyl bornanesultam derivative **22** to provide target aldehyde **4**.[18]

With efficient synthetic access to compounds **3** and **4**, we next examined their joining via aldol bond construction (Table 1). Analysis of this double stereodifferentiating process dictated the use of enolborinates to provide for

Table 1. Aldol Reactions of Enolborinates Derived from **3**



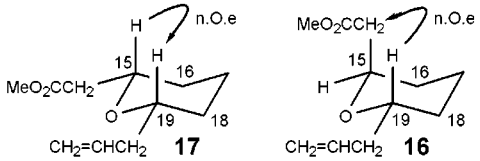
entry	RCHO	enolization	yield[a]	products (ratio)[b]
1	**4**	Chx_2BCl[c]	68%	**23a**:**24a** (1.5:1)
2	**4**	Bu_2BOTf[d]	45%	**23a**:**24a** (3:1)
3	**4**	Et_2BOTf[c]	86%	**23a**:**24a** (5.5:1)
4	EtCHO	Chx_2BCl[c]	87%	**23c**:**24c** (1.8:1)
5	EtCHO	Bu_2BOTf[d]	91%	**23c**:**24c** (3:1)
6	EtCHO	Et_2BOTf[d]	91%	**23c**:**24c** (5:1)
7	*epi*-**4**	Chx_2BCl[c]	66%	**23b**:**24b** (1.4:1)
8	*epi*-**4**	Bu_2BOTf[d]	90%	**23b**:**24b** (2.4:1)
9	*epi*-**4**	Et_2BOTf[d]	90%	**23b**:**24b** (3.4:1)

[a] Isolated yield of aldol adducts. [b] Ratios determined by ^{1}H NMR analysis (entries 1−3) or HPLC (entries 4−9) of the unpurified product mixture. [c] Enolization with Et_3N. [d] Enolization with *i*-Pr_2NEt.

maximum stereocontrol via 1,5-*anti* asymmetric induction.[19] Disappointingly, the use of dicyclohexyl or dibutyl enolborinates derived from **3**[20] in combination with aldehyde **4** provided aldol products with low levels of diastereoselection (**23a**:**24a** = 1.5:1 and 3:1 respectively, entries 1−2).[21] We noticed, however, that the selectivity was inherently better with the smaller dibutyl enolborinate, encouraging us to engage the diethyl enolborinate derived from **3**.[22] Indeed, reaction of aldehyde **4** with this enolborinate proceeded with an increased level of diastereoselectivity (**23a**:**24a** = 5.5:1, entry 3). These results raise two important questions: (1) what is the reason for the reduced selectivity as compared to the examples reported by the Evans and Patterson groups and (2) what is the origin of the boron ligand effect on reaction stereoselectivity? To answer these questions, we had to dissect the influence of aldehyde structure on the stereoselectivity of reactions with enolborinates derived from methyl ketone **3**. As indicated by the similar selectivities obtained for the aldol reactions of **3** with propionaldehyde

(14) The *trans*-isomer **16** predominated when the reaction was conducted at −78 °C (see also: Schneider, C.; Schuffenhauer, A. *Eur. J. Org. Chem.* **2000**, 73−82).

(15) The stereochemistry was assigned on the basis of ^{1}H NMR coupling constants and NOE experiments (**17**, $^3J_{H15-H16e}$ = 1.6 Hz, $^3J_{H15-H16a}$ = 10.8 Hz, $^3J_{H19-H18e}$ = 1.6 Hz, $^3J_{H19-H18a}$ = 10.8 Hz; **16**, $^3J_{H15-H16e}$ = 3.6 Hz, $^3J_{H15-H16a}$ = 6.4 Hz, $^3J_{H19-H18e}$ = 3.6 Hz, $^3J_{H19-H18a}$ = 8.8 Hz).



(16) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpí, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047−1049.

(17) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059−4065.

(18) Oppolzer, W.; Darcel, C.; Rochet, P.; Rosset, S.; De Brabander, J. *Helv. Chim. Acta* **1997**, *80*, 1319−1337. A two-step reduction/oxidation sequence is more convenient for a large scale preparation of aldehyde **4** (see Supporting Information).

(19) (a) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788−789. (b) Paterson, I.; Gibson, K. R.; Oballa, R. M. *Tetrahedron Lett.* **1996**, *37*, 8585−8588.

(20) For examples of excellent 1,5-*anti* stereoinduction by a *β*-tetrahydropyranyl moiety, see: (a) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033−10046. (b) Kozmin, S. A. *Org. Lett.* **2001**, *3*, 755−758.

(21) The inferred[19,20] 1,5-*anti* stereochemical relationship in **23a** was confirmed by assigning the absolute configuration at C11 via the Mosher ester method (see Supporting Information): Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.

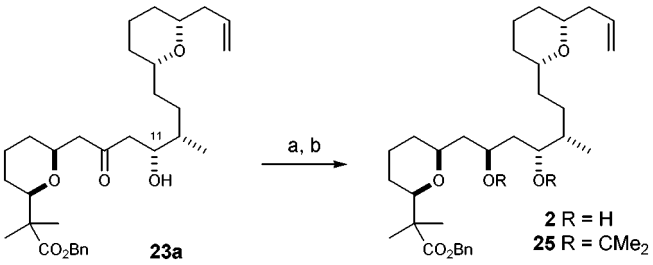
(22) Changes in the size of boron substituents have been shown to influence the diastereoselectivity of methyl ketone aldol reactions with α-Me-*β*-alkoxy aldehydes: Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443−3446.

and **4** (Table 1, entries 4−6 vs entries 1−3), there are no substantial additional nonbonded interactions imposed by the anti-Felkin arrangement of the α-Me group of aldehyde **4** in the transition state, demonstrating that the reaction diastereoselectivity is the result of the intrinsic facial bias of the enolborinate partner.[23] In contrast, nonbonded interactions between the methyl ketone substituent and the α-Me substituent of aldehyde *epi*-**4**[24] in a Felkin orientation are most likely responsible for the lower selectivities tabulated in entries 7−9.[23,25]

Perhaps more importantly, the set of experiments described in Table 1 features the general dependence of aldol 1,5-stereoinduction on the size of the enolborinate ligands, irrespective of aldehyde structure.[26] Thus, reactions with the smaller diethyl enolborinates are always more selective for the 1,5-*anti* aldol products **23a**−**c** than the corresponding reactions with dibutyl and dicyclohexyl enolborinates. Without a proper knowledge of the reacting conformation of the enolborinates and the integrity of a presumed twist-boat transition state, it is premature to speculate on the origin of the boron ligand effect in these aldol reactions.[27]

The final step for the synthesis of the C1−C21 (C1′−C21′) fragment **2** required an *anti*-selective reduction of *β*-hydroxy ketone **23a** (Scheme 3). For practical reasons, the mixture of aldolates was reduced with $Me_4NBH(OAc)_3$ to give *anti* diol **2** in 82% isolated yield, together with two minor diastereomeric diols (12%).[28] The 1,3-*anti* diol stereochemistry was confirmed by ^{13}C NMR analysis of the corresponding acetonide **25** (isopropylidene carbon resonances at 24.6, 25.4 and 100.3 ppm).[29]

Scheme 3[a]



[a] Reagents and conditions: (a) $Me_4NBH(OAc)_3$, HOAc, MeCN, −10 °C (82%); (b) Me_2CO, $Me_2C(OMe)_2$, CSA, rt (67%).

In summary, we have accomplished a highly efficient and stereoselective synthesis of the C1−C21 (C1′−C21′) fragment of SCH 351448 in 17 total steps (10 steps longest linear sequence; 14% overall yield) from readily available materials **5** and **14**. We also have observed an interesting boron ligand effect on the stereoselectivity of aldol reactions with methyl ketone-derived enolborinates. With all the stereochemical issues solved, we are now in a position to explore the final steps of the synthesis, which include incorporation of an ortho-substituted salicylic acid fragment and dimerization to obtain the natural product.

Acknowledgment. Financial support provided by the Robert A. Welch Foundation, the National Institutes of Health (CA 90349), and junior faculty awards administered through the Howard Hughes Medical Institute and the University of Texas Southwestern Medical Center is gratefully acknowledged. HRMS analyses were performed at the NIH regional mass spectrometry facility at the University of Washington, St. Louis, MO. J. K. De Brabander is a fellow of the Alfred P. Sloan Foundation.

Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) It has been postulated that twist-boat transition structures are preferred in aldol reactions with methyl ketone-derived enolborinates, see refs19, 22, and (a) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481−493. (b) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576−3581. (c) Bernardi, F.; Robb, M. A.; Suzzi-Valli, G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1991**, *56*, 6472−6475.

(24) The C12-epimer of aldehyde **4** (*epi*-**4**) was synthesized from aldehyde **19** by following the protocol outlined in Scheme 2 with the exception of the use of enantiomeric (2*R*)-*N*-propionyl bornanesultam for the installation of the C12-stereocenter.

(25) Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Tetrahedron Lett.* **1993**, *34*, 8387−8390.

(26) Roush has formulated a hypothesis to rationalize the steric effect of metal enolate ligands with the aldehyde component, see ref 22.

(27) A detailed study to rationalize the boron ligand effect and explore its scope will be reported in due course. At present, we speculate that the smaller boron ligands have a larger intrinsic (i.e., irrespective of aldehyde or enolate structure) preference for the twist-boat transition structure. Both ab initio calculations[19a,23a] and force field models[23b] have indicated that a B-H → B-Me substitution decreases the energy gap between twist-boat and chair transition states.

(28) The separation of **23a** from **24a** requires preparative HPLC, in contrast to the corresponding reduced products, which could be conveniently separated by flash chromatography.

(29) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.