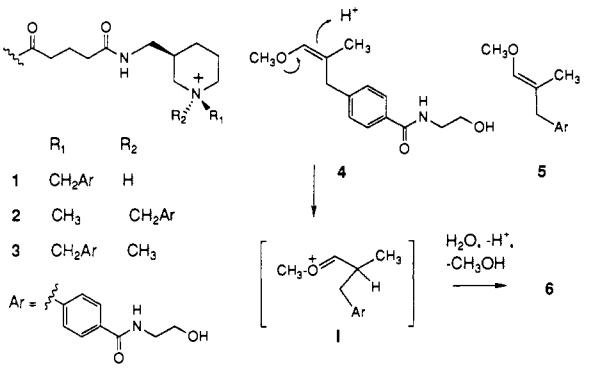


Figure 1. Structures of the racemic haptens **1**, **2**, and **3**,[8] prochiral enol ether substrates **4** and **5**, and their hydrolysis via oxocarbonium ion I.[7]

Table I. Kinetic Parameters of Antibody 14D9 for Substrates **4**, **5**, and **7**

substrate	K_m, 10^{-6} M	k_{cat}, s^{-1}	k_{cat}/k_{uncat}	ee, %[c]
4[a]	340	9.5×10^{-5}	2500	96
5[a]	130	8.3×10^{-6}	290	93
7[b]	100	7.8×10^{-5}	70	

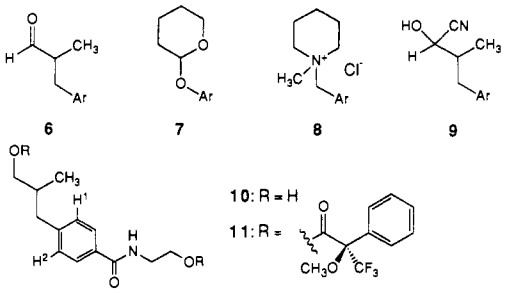
[a] Conditions: 100 mM MES (morpholinylethanesulfonic acid) buffer, pH 5.7, 100 mM NaCl, 37 °C.[10] [b] Assayed in the same buffer at 20 °C.[8] [c] Determined by ^{1}H NMR analysis of the Mosher ester **11**.[10,11] The absolute configuration of the product was not determined.

under acidic conditions proceeds by rate-determining carbon protonation and is catalyzed by carboxylic acids.[7] We reasoned that the carboxyl groups expected in the binding sites of antibodies raised against the cationic haptens **1**, **2**, and **3**[8] should be in an optimal position to assist carbon protonation of enol ethers **4** and **5** (Figure 1). Furthermore, binding interactions to the tetrahedral ammonium center should favor pyramidalization of the trigonal carbon atom undergoing protonation.

Antibodies to haptens **1**, **2**, and **3**[8] were assayed against substrates **4** and **5** for production of aldehyde **6**.[9] Seven out of 15 antibodies against **1**, 13 out of 23 antibodies against **2**, and 12 out of 22 antibodies against **3** catalyzed the hydrolysis of both **4** and **5**. Antibody 14D9, an antibody against **2** which also catalyzed the hydrolysis of acetal **7**,[8] showed a remarkable activity for the cleavage of enol ethers **4** and **5** and was investigated further. The antibody-catalyzed formation of **6** followed Michaelis-Menten kinetics for both **4** and **5** (Table I). In both cases, potent inhibition by the achiral hapten analogue **8** allowed quantitative assignment of the catalytic activity to the antigen combining site[9] (Chart I).

The enantiomeric purity of aldehyde **6** was determined by reduction to alcohol **10** and derivatization to the Mosher ester **11**. The diastereomeric purity of **11** was measured by ^{1}H NMR integration of the aromatic protons H^1 and H^2 (500 MHz, $CDCl_3$, δ 7.10 (major) and 7.13 ppm (minor)). To prevent racemization of the product, the reaction was run in a cyanide buffer, which allowed reversible, quantitative protection of **6** as the cyanohydrin **9**.[10] Under these conditions, the measured diastereomeric ratio of the Mosher esters **11** was 50:1, corresponding to an enantiomeric excess of 96% ee. When **5** was used as a substrate, the same

Chart I



enantiomer was obtained with 93% ee.[11]

In conclusion, an antibody capable of nearly completely enantioselective enol ether protonation has been obtained from a hapten where a positively charged tetrahedral nitrogen atom is substituted for the trigonal β-carbon atom. The high proportion of catalytic antibody clones suggests that our hapten design should be quite general and thus applicable to other enol ether structures. Efforts are now being directed toward the understanding of the mechanism of action of this new catalyst.

Supplementary Material Available: Experimental procedures for the syntheses of **4**, **5**, **6**, and **11** (2 pages). Ordering information is given on any current masthead page.

(11) In both cases, the antibody reaction proceeds with very high enantiofacial selectivity of protonation, its efficiency being limited by the relatively modest efficiency of the catalyst. By applying the kinetic constants of 14D9 (Table I) to the preparative assay conditions, the level of racemic product from the background reaction can be estimated to be 1.5% with **4** and 5% with **5**. The effective selectivity for the antibody reaction with **4** and **5** is thus approximately 97.5% ee and 98% ee, respectively.

(7) (a) Chiang, Y.; Kresge, A. J. *J. Chem. Soc. B* **1967**, 53. (b) Kresge, A. J.; Segatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228. (c) Kresge, A. J.; Chiang, Y. *Science* **1991**, *253*, 395.

(8) Reymond, J.-L.; Janda, K. D.; Lerner, R. A. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1711.

(9) The binding of **8** to antibody 14D9 is illustrated by the following experiment:[8] A 4 μM solution of 14D9 was completely inhibited by 10 μM of **8**. After 5 days of extensive dialysis at 37 °C, the inhibited antibody sample recovered only 40% of the activity of a noninhibited control sample.

(10) Assay conditions: 20 μM antibody, 1 mM substrate, 50 mM Bis-tris pH 6.0, 100 mM NaCl, 37 °C. Formation of the aldehyde was followed by HPLC (Asahipac ODP-50 RP C-18, 77% H_2O, 33% CH_3CN, 0.8 mL min^{-1}, t_R = 6.1 min) against an internal standard (2-acetamidophenol, t_R = 8.5 min). Preparative assay: 50 mM MES, pH 5.6, 100 mM NaCl, 10 mM HCN, 20 μM 14D9, 5 mL. **4**: 300 μM (respectively, **5**: 200 μM). Incubation at 37 °C for 3 days (7 days) gave approximately 40% (20%) conversion of **4** (**5**) to cyanohydrin **9** (mixture of isomers).

Toward the Development of a General Chiral Auxiliary. 1. Preparation of a New Class of Camphor Lactam Imides and Their Application to the Construction of Quaternary Centers via Diels-Alder Cycloaddition

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Efforts to control absolute stereochemistry in both inter- and intramolecular variants of the Diels-Alder reaction via Lewis acid promoted cycloadditions employing chiral dienophiles or catalysts have recently enjoyed considerable success.[1-3] However, a significant limitation was apparent when we attempted to apply these methods to the construction of quaternary carbon centers.[4] Very few examples have been documented,[1c,2,3b] although concurrent efforts in other laboratories have also elegantly addressed this

(1) (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969. (b) Tomioka, K. *Synthesis* **1990**, 541. (c) Masamune, S.; Reed, L. A., III; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441. (d) Busacca, C. A.; Meyers, A. I. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2299. (e) Kouklovsky, C.; Pouilhès, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672. (f) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (g) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimoru, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.

(2) (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261.

(3) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397. (b) Chapuis, C. Ph.D. Dissertation No. 2144, University of Genève, Genève Switzerland, 1984.

(4) Fang, Y. Ph.D. Dissertation, University of Rochester, Rochester, NY, 1991. For two cases of successful cycloadditions of α-substituted dienophiles bearing these auxiliaries, see refs 2a and 3b.

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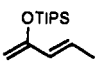
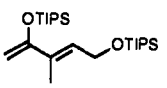
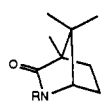
Table I[a-c]

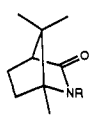
dienophile	diene	π-facial selectivity	endo/exo	yield (%)
3		91:9[d]	90:10	93
3		85:15[e]		61
3		90:10		79
3		95:5		82
3		90:10	67:33	63
3	 OTIPS	57:43[f]		89
3	 OTIPS	50:50[f]	87:13	91
3[g]	 OTIPS OTIPS	88:12[h-j]	>98:2	95
4		95:5		82
4		~95:5	92:8	97
4		96:4		83

[a] All reactions were conducted with excess diene [alkyl (5–10 equiv), oxygenated (1.2 equiv)] in the presence of 1.5 equiv of methylaluminum dichloride in CH_2Cl_2 at ~0.25 M in dienophile at −78 °C unless otherwise indicated. [b] Diastereomer ratios determined by capillary GLC. [c] Yields refer to isolated yields of chromatographically homogeneous material. [d] Reaction conducted at −90 °C. [e] Reaction conducted at −30 °C. [f] Diethylaluminum chloride (DEAC) employed. [g] ent-**3** was used in this experiment. [h] $TiCl_4$ employed. [i] The Lewis acid is added very slowly to a mixture of diene and dienophile. [j] Reaction conducted at −20 °C.

problem.[5] We sought to design a more general chiral auxiliary whose derived α- and β-substituted chiral dienophiles, the former suitable for generation of quaternary carbons, would exhibit high diastereofacial selectivity in Lewis acid promoted Diels–Alder cycloaddition reactions. The wide range of uses of chiral auxiliaries and catalysts underscores the need to identify auxiliaries which function effectively in a spectrum of applications.[1,3-5] Toward this goal, this communication details the preparation and use of camphor lactams **1** and **2** as the derived methacrylate and crotonate carboximides **3–6** for diastereofacial discrimination in Diels–Alder cycloadditions.

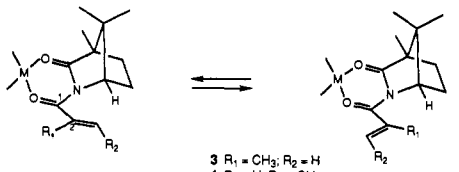


1 R = H
3 R = CH_2=C(CH_3)C(O)-
4 R = (E)CH_3CH=CHC(O)-



2 R = H
5 R = (E)CH_3CH=CHC(O)-
6 R = CH_2=C(CH_3)C(O)-

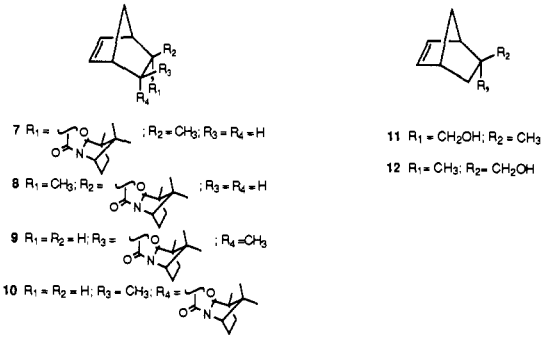
Existing auxiliaries of the imide type function effectively as the result of structural features which enhance reactivity while imparting conformational restrictions to (1) rotation about the C_1–N_{aux} bond via chelation with a Lewis acid and (2) rotation about the C_1–C_2 bond (s-cis or s-trans amide) via allylic strain.[1-4] We sought to retain and exploit these essential features while altering the rotational preference about the C_1–C_2 bond, thereby removing detrimental nonbonded interactions in α-substituted dienophiles. Our choice of lactams **1** and **2** was predicated upon preliminary molecular modeling of imides **3–6** (eq 1), which suggested that **3** would preferentially adopt the s-trans rotamer about the C_1–C_2 bond, whereas **4** and **5** would prefer the s-cis rotamer and **6** would be unselective.[6,7]



3 R_1 = CH_3; R_2 = H
4 R_1 = H; R_2 = CH_3

(1)

To validate this model, the requisite lactams **1** and **2** were prepared and converted to the derived α,β-unsaturated carboximides **3–6** via acylation of the Na salts of **1** and **2** (NaH, THF, 0 °C) with the appropriate acid chloride (77–90% yield).[8-10] Since we felt that generation of quaternary carbon centers would be among the most stringent tests of these new dienophiles, we examined the reactions of **3** and **4** with a variety of common alkyl-substituted dienes (Table I). Reaction of **3** with cyclopentadiene, the prototypical test case, in the presence of CH_3AlCl_2 (1.5 equiv)[2b] in CH_2Cl_2 at −90 °C afforded a mixture of the four possible cycloadducts **7–10** (82:9:5:4) in 98% yield.[11] The



7 R_1 = ; R_2 = CH_3; R_3 = R_4 = H
8 R_1 = CH_3; R_2 = ; R_3 = R_4 = H
9 R_1 = R_2 = H; R_3 = ; R_4 = CH_3
10 R_1 = R_2 = H; R_3 = CH_3; R_4 =

11 R_1 = CH_2OH; R_2 = CH_3
12 R_1 = CH_3; R_2 = CH_2OH

structure and absolute stereochemistry of the major adduct, obtained by crystallization, was confirmed by single-crystal X-ray analysis.[12] In accord with our expectation, **7** arises via endo addition to the s-trans rotamer of **3** from the less hindered face of the camphor system (opposite the 1-carbon bridge).[6] Exo/endo selectivity was evaluated by removal of the chiral auxiliary (LAH/Et_2O) to afford a mixture of two alcohols, **11** and **12** (86:14). Thus, π-facial selectivity can be established as 91:9 (82% de).

Examination of the entries in Table I establishes a general pattern of selectivity in the range of 80–92% de for a variety of acyclic alkyl-substituted dienes, including butadiene, isoprene, 2,3-dimethylbutadiene, and piperylene, affording the major cycloadducts **13–16**.[13] As with cyclopentadiene, the exo/endo selectivity is variable and invariably less than is seen with crotonate type systems both in the literature and in our studies (vide infra).[1-3,14] In general, the major diastereomer can be readily

(5) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481.

(6) Molecular modeling was performed using MacroModel (C. Still, Columbia University) and the Tektronix CaChe system both using MM2, MM3, and proprietary parameter sets (CaChe). s-Trans rotamers have been previously documented and their possible role discussed: Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Lett.* **1988**, *29*, 3559.

(7) Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365.

(8) Both antipodes of lactam **1** were prepared from the appropriate antipode of camphor in five steps (55% overall yield) by improved variants of literature procedures.[9] Similarly, the antipodes of **2** were prepared in four steps from the appropriate antipode of camphoric acid (78% overall yield).[10] Details are provided in the supplementary material.

(9) Noyes, W. A.; Potter, R. S. *J. Am. Chem. Soc.* **1915**, *37*, 189.

(10) Noyes, W. A.; Nickell, L. F. *J. Am. Chem. Soc.* **1914**, *36*, 118 and ref 9.

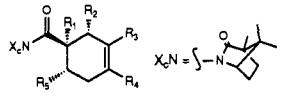
(11) A number of Lewis acids were screened, including Et_2AlCl, $SnCl_4$, and $TiCl_4$. CH_3AlCl_2 was determined to be overall the most satisfactory in terms of rate, yield, and de among those examined to date.

(12) Nelson, S. G. Ph.D. Dissertation, University of Rochester, Rochester, NY, 1991.

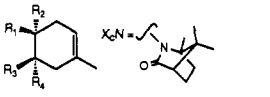
(13) For acyclic dienes not bearing substituents on the terminal carbons, π-facial selectivity and endo/exo selectivity cannot be distinguished. Thus, the observed products could also arise via one of several alternative transition states (s-trans/syn to 1C bridge or s-cis/anti to 1C bridge).

isolated by chromatography and the auxiliary removed in high yield (80–95%) via treatment with $LiOH/H_2O_2$ to afford the acid or LAH to afford the alcohol with excellent recovery of auxiliary (>90%).[3,15]

Remarkably, in view of the modeling results and prior experience, reaction of the crotonate dienophile **4** with isoprene afforded the major cycloadduct **17** (96:4) possessing the unexpected absolute configuration which apparently arises via the s-trans rotamer of **4** as does **14** from **3**.[16,17] Other dienes gave π-facial selectivity (90–92% de) comparable to that seen for the Evans and Oppolzer auxiliaries with the same dienes.[1-3] However, reaction of dienophiles **5** and less surprisingly **6** with isoprene afforded mixtures of adducts **18–19** and **20–21**. Predictably poor π-facial selectivity is observed (~1:1), presumably owing to loss of control over the rotamer population about the C_1–C_2 bond.

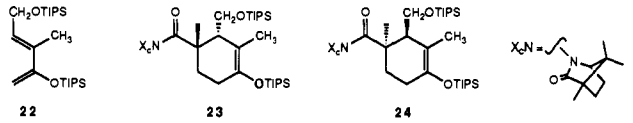


13 $R_1 = CH_3$; $R_2 = R_3 = R_4 = R_5 = H$
14 $R_1 = CH_3$; $R_2 = R_3 = H$; $R_4 = CH_3$; $R_5 = H$
15 $R_1 = CH_3$; $R_2 = H$; $R_3 = R_4 = CH_3$; $R_5 = H$
16 $R_1 = R_2 = CH_3$; $R_3 = R_4 = R_5 = H$
17 $R_1 = R_2 = R_3 = H$; $R_4 = R_5 = CH_3$



18 $R_1 = CONX_C$; $R_2 = CH_3$; $R_3 = R_4 = H$
19 $R_1 = CH_3$; $R_2 = CONX_C$; $R_3 = R_4 = H$
20 $R_1 = H$; $R_2 = CONX_C$; $R_3 = CH_3$; $R = H$
21 $R_1 = CONX_C$; $R_2 = H$; $R_3 = H$; $R_4 = CH_3$

Somewhat surprisingly, there have been relatively few reported examples of Lewis acid catalyzed cycloadditions of chiral dienophiles with oxygen-substituted dienes, probably as the result of instability of these dienes to the required Lewis acids.[1-4] We have employed triisopropylsilyl (TIPS) protected oxygenated dienes, which has permitted successful cycloadditions with **3–5** in the presence of Et_2AlCl in high yield (89–95%).[13,18] However, as shown in Table I, several TIPS-protected dienes were examined which uniformly exhibited substantially lower π-facial selectivities (1–2:1) than the comparably substituted alkyl dienes. This surprising lack of selectivity may result as a consequence of a very early reactant-like transition state for the cycloaddition reactions involving oxygen-substituted dienes. Thus, the distance-dependent nonbonded interactions normally responsible for the energetic differences which result in π-facial selectivity are much smaller. Significantly, reaction of ent-**3** with the somewhat less reactive and sterically more encumbered diene **22** (2.0 equiv) in the presence of $TiCl_4$ afforded a mixture of the two endo cycloadducts **23** and **24** (88:12) exclusively. The stereochemistry and absolute configuration of **23** was confirmed by X-ray analysis of the derived ketone.[19]



22 **23** **24**

It is interesting to note that the level of diastereoselection in all of these cycloadditions appears to correlate with the diene structure and that the highest π-facial selectivities are observed with dienes bearing substitution at both internal carbons. The generality and possible mechanistic significance of this observation as well as the structure of the reactive dienophile–Lewis acid complexes in solution with respect to the C_1–C_2 rotamer(s) and the development of a more accurate model for the transition-state structure are under investigation. Further studies of cycloaddition reactions of these new chiral dienophiles are also in progress as are studies of the applicability of these auxiliaries to a variety of other reactions amenable to use for asymmetric synthesis.

Acknowledgment. We are extremely grateful to the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health for a research grant (GM-29290) in support of these studies. We also wish to acknowledge fellowship support awarded to S.G.N. provided by the Merck Co.

Supplementary Material Available: Experimental details for preparation of **1** and **2** and a general procedure for the asymmetric Lewis acid catalyzed Diels–Alder cycloaddition (7 pages). Ordering information is given on any current masthead page.

(14) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.
(15) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.
(16) The absolute configuration of these adducts was established by correlation with known substances: Sonnet, P. E.; McGovern, T. P.; Cunningham, R. T. *J. Org. Chem.* **1984**, *49*, 4639 and refs 1–3.
(17) This result could also arise by reaction of **4** via other endo and exo transition states both chelated and nonchelated. Since exo/endo selectivity is dependent on the stoichiometry of the Lewis acid, a chelated Lewis acid dienophile complex seems implicated.[2]
(18) Independently, Overman and co-workers have made similar observations: Early, W. G.; Jacobsen, J.; Meier, G. P.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3781. Devine, P. N.; Oh, T. *J. Org. Chem.* **1991**, *56*, 1955.
(19) Details of the single-crystal X-ray analyses of **7** and **23** will appear in a forthcoming full account of these studies.

Asymmetric Synthesis of the Macrolide (+)-A83543A (Lepicidin) Aglycon

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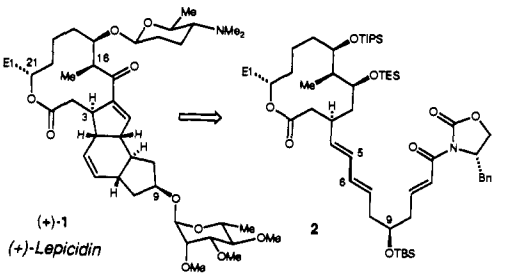
Received December 4, 1991

This communication reports the first synthesis of the structurally unique macrolide A83543A,[1] for which we suggest the name lepicidin. This new natural product has been shown to have potent insecticidal activity, particularly against Lepidoptera larvae.[2] At the time that this project was initiated, the absolute configuration of lepicidin was unknown; consequently, the absolute configuration shown here was presumed on the basis of biogenetic considerations.[3] The synthetic plan for (+)-**1** (Scheme I) was designed around the illustrated intramolecular Diels–Alder[4] reaction of **2**,

Scheme I



which was assembled from a lactonic fragment **3** (Scheme II) and dienic imide **4** (Scheme III) via palladium-catalyzed cross coupling

(1) Kirst, H. A.; Michel, K. H.; Martin, J. W.; Creemer, L. C.; Chio, E. H.; Yao, R. C.; Nakatsukasa, W. M.; Boeck, L. D.; Occolowitz, J. L.; Paschal, J. W.; Deeter, J. B.; Jones, N. D.; Thompson, G. D. *Tetrahedron Lett.* **1991**, *32*, 4839–4842.
(2) Boeck, L. D.; Chio, H.; Eaton, T. E.; Godfrey, O. W.; Michel, K. H.; Nakatsukasa, W. M.; Yao, R. C. Eli Lilly and Co. Eur. Pat. Appl. 375316, 1990; *Chem. Abstr.* **1991**, *114*, 80066.
(3) The polycyclic ring system in ikarugamycin bears a close structural relationship to lepicidin: Jomon, K.; Kuroda, Y.; Ajisaka, M.; Sakai, H. *J. Antibiot.* **1972**, *25*, 271. Total syntheses of ikarugamycin: (a) Boeckman, R. K.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036–8037. (b) Paquette, L. A.; Macdonald, D.; Anderson, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 9292–9299.
(4) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.

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