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Synthesis of (−)-Agelastatin A by [3.3] Sigmatropic Rearrangement of Allyl Cyanate

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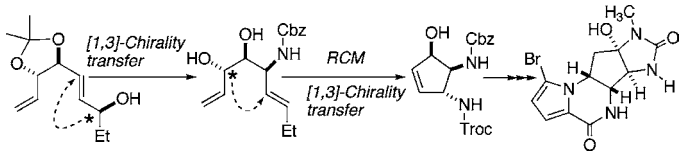
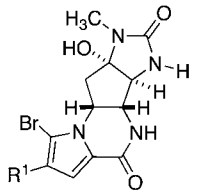
ABSTRACT



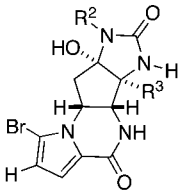
Total synthesis of (−)-agelastatin A has been achieved starting from L-arabitol. The highlights in our synthesis include the preparation of vicinal diamine moiety by [3.3] sigmatropic rearrangement of allyl cyanate and construction of central ring-C with ring-closing metathesis.

In 1991, one of us reported that dehydration of allyl carbamates generates allyl cyanates, which immediately undergo isomerization to the allyl isocyanates.[1] In an effort to expand the scope and synthetic usefulness of this novel reaction in the context of an allyl amine synthesis, we performed mechanistic studies and confirmed that isomerization of the allyl cyanate is a concerted process involving a six-membered cyclic transition state with a high degree of [1,3]-chirality transfer.[2] As a consequence, the [3.3] sigmatropic rearrangement of allyl cyanates has been widely accepted by the synthetic community as a useful tool for allyl amine syntheses.[3]

To advance further the utility of this rearrangement, we recently established a new protocol for stereoselective allyl amine synthesis.[4] We also developed a new approach to a stereocontrolled synthesis of vicinal diamine.[5] Further investigations to construct 1,2-diamino moieties led us to explore the synthesis of marine alkaloid, (−)-agelastatin A. In 1993 Pietra and co-workers reported their isolation of the novel alkaloids, (−)-agelastatin A (**1**) and its minor congener agelastatin B (**2**) from the deep water marine sponge *Agelas dendromorpha* collected in the Coral Sea near New Caledonia.[6] A series of degradation and spectroscopic experiments established the structure and relative stereochemistry of these alkaloids, which feature an array of four nitrogen-substituted stereogenic centers around a central cyclopentane ring. Two closely related metabolites, agelastatin C (**3**) and D (**4**), were later isolated by Molinski et al. from the sponge *Cymbastela* sp. collected at Muiron Island in West Australia.[7]



agelastatin A (**1**) R^1 = H
agelastatin B (**2**) R^1 = Br



agelastatin C (**3**) R^2 = Me, R^3 = OH
agelastatin D (**4**) R^2 = H, R^3 = H

The architecturally unusual tetracyclic array, coupled with significant biological activity and scarce availability from

(1) Ichikawa, Y. *Synlett* **1991**, 238.
(2) (a) Ichikawa, Y.; Tsuboi, K.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791. (b) Ichikawa, Y.; Yamauchi, E.; Isobe, M. *Biosci. Biotechnol. Biochem.* **2005**, *69* (5), 939.
(3) (a) Kapfere, P.; Sarabia, F.; Vassela, A. *Helv. Chim. Acta* **1999**, *82*, 645. (b) Roulland, E.; Monneret, C.; Florent, J.-C. *J. Org. Chem.* **2002**, *67*, 4399. (c) Roy, S.; Spino, C. *Org. Lett.* **2006**, *8*, 939.
(4) (a) Ichikawa, Y.; Ito, T.; Nishiyama, T.; Isobe, M. *Synlett* **2003**, 1034. (b) Ichikawa, Y.; Ito, T.; Isobe, M. *Eur.−J. Chem.* **2005**, 1949.
(5) Ichikawa, Y.; Egawa, H.; Ito, T.; Isobe, M.; Nakano, K.; Kotsuki, H. *Org. Lett.* **2006**, *8*, 5737.
(6) For the isolation and biological activities of (−)-agelastatin A: (a) D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305. (b) D'Ambrosio, M.; Guerriero, A.; Chiasera, G.; Pietra, F. *Helv. Chim. Acta* **1994**, *77*, 1895. (c) D'Ambrosio, M.; Guerriero, A.; Ripamonti, M.; Debitus, C.; Waikedre, J.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 727.
(7) Hong, T. W.; Jimenez, D. R.; Molinski, T. F. *J. Nat. Prod.* **1998**, *61*, 158.

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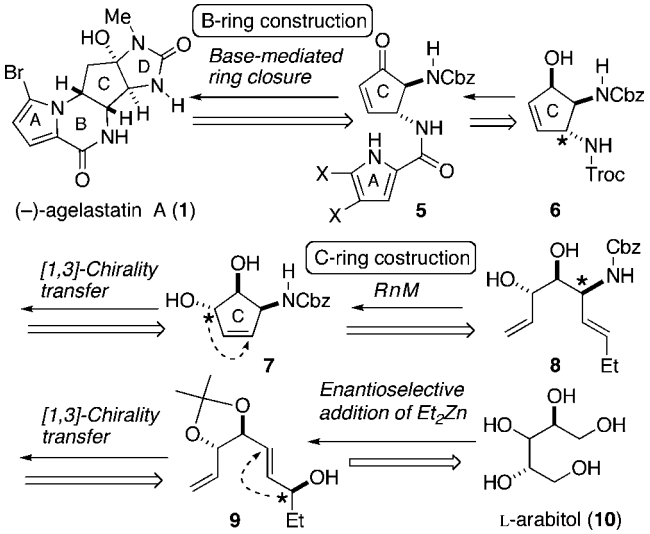
marine organisms, has already stimulated the synthetic community, and several total synthesis of **1** have been reported. The first total synthesis of (±)-agelastatin A was announced by a group of Weinreb, who employed a novel hetero-Diels−Alder cycloaddition reaction and a Sharpless/Kresze allylic amination sequence for assembly of the cyclopentane core.[8] Feldman and Saunders subsequently reported an enantioselective route to (−)-agelastatin A and B that exploited a unique vinylcarbene C−H insertion sequence for the preparation of the cyclopentane ring.[9] A formal asymmetric synthesis of (−)-**1** was accomplished by Hale et al. in their enantioselective synthesis of Weinreb's intermediate using ring-closing metathesis (RCM) of 3,4-diamino-1,5-diene as a substrate, which was prepared from Hough−Richardson aziridine. This group later described the total synthesis of (−)-agelastatin A (**1**) from a chiral bicyclic cyclopentene oxazolidinone intermediate using a new strategy.[10] The synthesis of Davis and Deng is based upon the sulfinimine-mediated enantioselective synthesis of *syn*-α,β-diamino ester and RCM.[11] Recently, a unique approach to the synthesis of **1** was reported by Trost and Dong, who employed palladium-catalyzed asymmetric allylic alkylation using pyrroles as nucleophiles.[12] In each of these syntheses, construction of the array of nitrogen substituted stereogenic centers around central cyclopentane core proved to be the critical problem for the successful syntheses.

In our retrosynthetic route to **1** (Scheme 1), it was

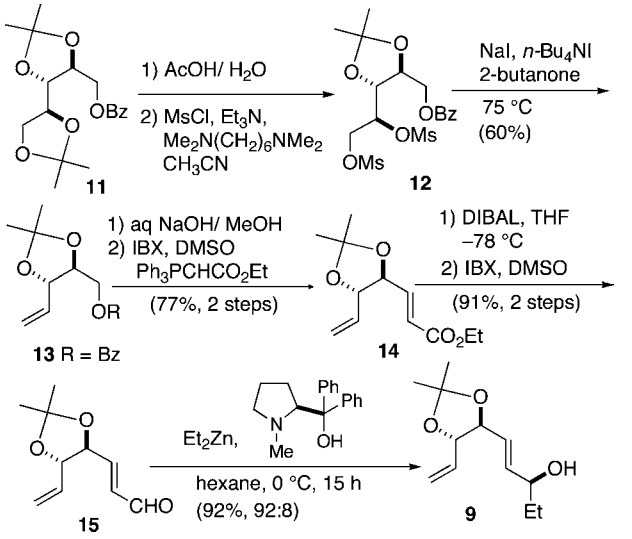
Scheme 1. Synthesis Plan for (−)-Agelastatin A



envisioned that construction of ring-B could be accomplished using intramolecular Michael addition of pyrrole ring-A (**5** → **1**), which draws on the Weinreb, Feldman, and Hale syntheses. For an access to the 1,2-diamino moiety in α,β-diaminocyclopentene **6**, we reasoned that [1,3]-chirality transfer using [3.3] sigmatropic rearrangement of an allyl cyanate would be appropriate (**7** → **6** and **9** → **8**). RCM reaction could be used to build up the cyclopentene C-ring system (**8** → **7**), which would also set up the substrate for the [1,3]-chirality transfer reaction to construct the vicinal diamine moiety in **6**. Allyl alcohol **9** would be derived from L-arabitol (**10**) via a multistep pathway involving the selective protection of hydroxy groups, carbon chain extension using Wittig reaction, and enantioselective addition of diethylzinc. In this paper we report the successful application of this strategy to the total synthesis of agelastatin A.

We initiated the synthesis of agelastatin A (**1**) with the preparation of allyl alcohol **9** starting from benzoate **11** derived from L-arabitol (**10**)[13] (Scheme 2). Selective depro-

Scheme 2. Synthesis of Allyl Alcohol **9** from L-Arabitol



tection of the terminal acetonide in **11** with aqueous acetic acid followed by mesylation of the resultant diol[14] gave the dimesylate **12**, which upon treatment with sodium iodide and tetra-*n*-butylammonium iodide in 2-butanone at 75 °C afforded the alkene **13**: the overall yield for the three-step sequence was 60%.[15] Saponification of the benzoate **13** gave the volatile alcohol, which was successively treated with a mixture of *o*-iodoxybenzoic acid (IBX) and (carbethoxymethylene)-triphenylphosphorane in DMSO.[16] This one-pot, two-step sequence furnished the α,β-unsaturated ester **14** predominantly in 77% yield. DIBAL reduction of the ester

(8) (a) Stien, D.; Anderson, G. T.; Chase, C. E.; Koh, Y.; Weinreb, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 9574. (b) Anderson, G. T.; Chase, C. E.; Koh, Y-h.; Stien, D.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 7594.

(9) (a) Feldman, K. S.; Saunders, J. C. *J. Am. Chem. Soc.* **2002**, *124*, 9060. (b) Feldman, K. S.; Saunders, J. C. *J. Org. Chem.* **2002**, *67*, 7096.

(10) (a) Hale, K. J.; Domostoj, M. M.; Tocher, D. A.; Irving, E.; Scheinmann, F. *Org. Lett.* **2003**, *5*, 2927. (b) Domostoj, M. M.; Irving, E.; Scheinmann, F.; Hale, K. J. *Org. Lett.* **2004**, *6*, 2615.

(11) Davis, F. A.; Deng, J. *Org. Lett.* **2005**, *7*, 621.

(12) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2006**, *128*, 6054.

(13) Benzoate **11** was readily prepared from commercially available L-arabitol in 80% yield over two steps through acetonidation followed by protection of the resultant primary alcohol as benzoate. See, Bukhari, M. S.; Foster, A. B.; Lehmann, J.; Webber, J. M.; Westwood, J. H. *J. Chem. Soc.* **1963**, 2291.

(14) Yoshida, Y.; Shimonishi, K.; Sakakura, Y.; Okada, S.; Asao, N.; Tanabe, Y. *Synthesis* **1999**, 1633.

(15) Bladon, P.; Owen, L. N. *J. Chem. Soc.* **1950**, 598.

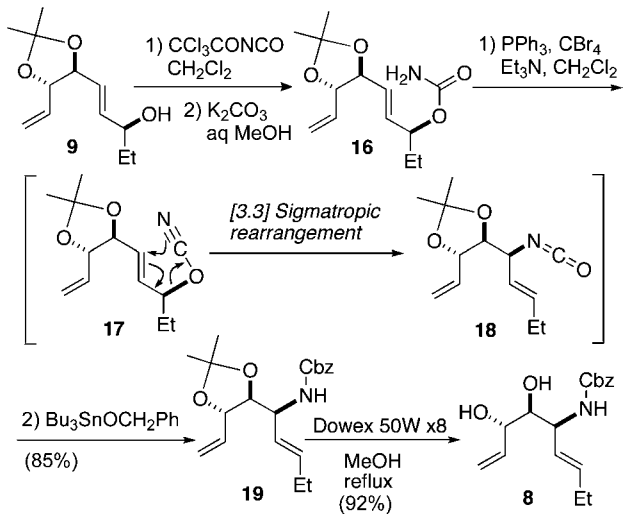
(16) Crich, D.; Mo, X. *Synlett* **1999**, 67.

14 and IBX oxidation of the resulting allyl alcohol gave the aldehyde **15** in 91% yield in two steps.

Enantioselective addition of diethylzinc to this α,β-unsaturated aldehyde **15** was carried out in the presence of the Soai catalyst (20 mol %) to provide allyl alcohol **9** in good yield (92%) with 92:8 selectivity as an inseparable diastereomeric mixture.[17] The structure of **9**, tentatively assigned by the Soai empirical rule, and was confirmed by Mosher−Kusumi MTPA ester analysis.[18]

Our first introduction of the nitrogen-substituted stereogenic center by [3.3] sigmatropic rearrangement of an allyl cyanate was achieved using allyl alcohol **9** as a substrate (Scheme 3). Reaction of **9** with trichloroacetyl isocyanate

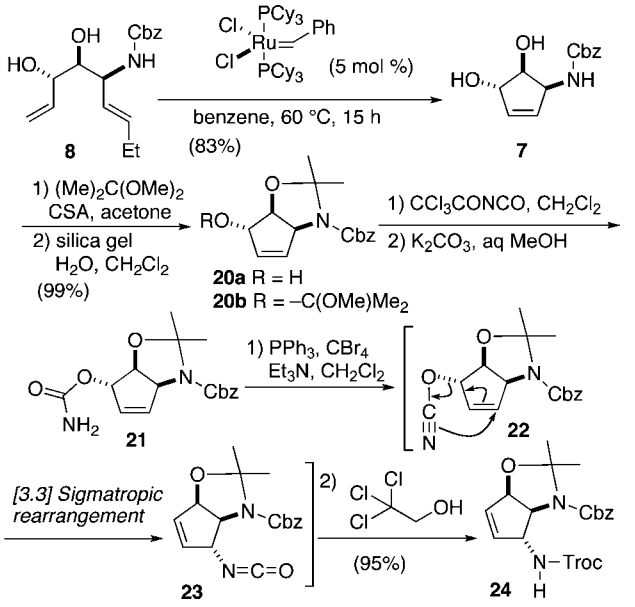
Scheme 3. [1,3]-Chirality Transfer of the Stereogenic Center in Allyl Alcohol **9**



followed by hydrolysis with aqueous potassium carbonate gave the allyl carbamate **16**. Dehydration of this carbamate with triphenylphosphine, carbon tetrabromide, and triethylamine in dichloromethane at −10 °C generated the allyl cyanate **17**,[19] which instantaneously rearranged into the allyl isocyanate **18** via a concerted cyclic transition state. To avoid a partial hydrolysis of the isocyanate function during aqueous workup, the reaction mixture was treated with tributyltin benzyl alkoxide. After workup and purification, this one-flask, three-step sequence furnished the Cbz-carbamate **19** in 85% overall yield from allyl alcohol **9**.[20] Finally, removal of the acetonide in **19** with Dowex 50W × 8 in refluxing methanol provided the diol **8** to set the stage for the next RCM.

We next faced the task of constructing the cyclopentene ring-C and the 2,3-diamino moiety (Scheme 4). The Grubbs

Scheme 4. Construction of the Cyclopentene Ring-C and 2,3-Diamino Moiety



catalyst is known to be tolerant of a wide range of functionality;[21] to our delight, RCM of the highly functionalized 1,6-diene **8** using first-generation ruthenium catalyst (5 mol %) took place smoothly at 60 °C over 15 h in benzene (0.01 M solution) to furnish the requisite cyclopentene ring-C **7** as a crystalline intermediate in good yield (83%).[22] The synthesis continued with the protection of **7** with 2,2-dimethoxypropane in the presence of *p*-TsOH to afford a mixture of **20a** and 1-methyl-1-methoxyethyl ether **20b**; the latter was hydrolyzed with wet silica gel, which set the stage for a second [1.3]-chirality transfer. The allyl alcohol **20a** was transformed into allyl carbamate **21**, and a one-pot, three-stage sequence involving dehydration, sigmatropic rearrangement (**22** → **23**), and trapping of the isocyanate with an appropriate alcohol were carried out as described in Scheme 3, except 2,2,2-trichloroethanol was employed for the de-

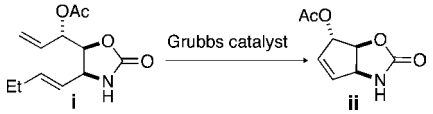
(17) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111.

(18) Ohtani, I.; Kusumi, K.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(19) This dehydration condition was first reported as a synthetic method for the preparation of isonitrile from formamide. See: Ichikawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2135.

(20) Addition of tributyltin alkoxide enhanced the yields of this in situ transformation of isocyanate into the corresponding carbamate. See: (a) Ichikawa, Y.; Osada, M.; Ohtani, I.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1449. (b) Bloodworth, A. J.; Davies, A. J. *J. Chem. Soc. C* **1965**, 5238. (c) Davies, A. *Synthesis* **1969**, 56.

(21) Our initial route focused on exploiting the fully protected 1,6-diene **i** as a substrate for RCM, because oxazolidinone ring was expected to induce turn-structure on the diene to facilitate the ring- closure process; in fact, cyclopentene **ii** was obtained in good yields. Unfortunately, we encountered difficulty associated with the manipulation of the carbamate group in **ii**, which revised our protecting group strategy. As a result, **8** was chosen as a substrate for RCM.

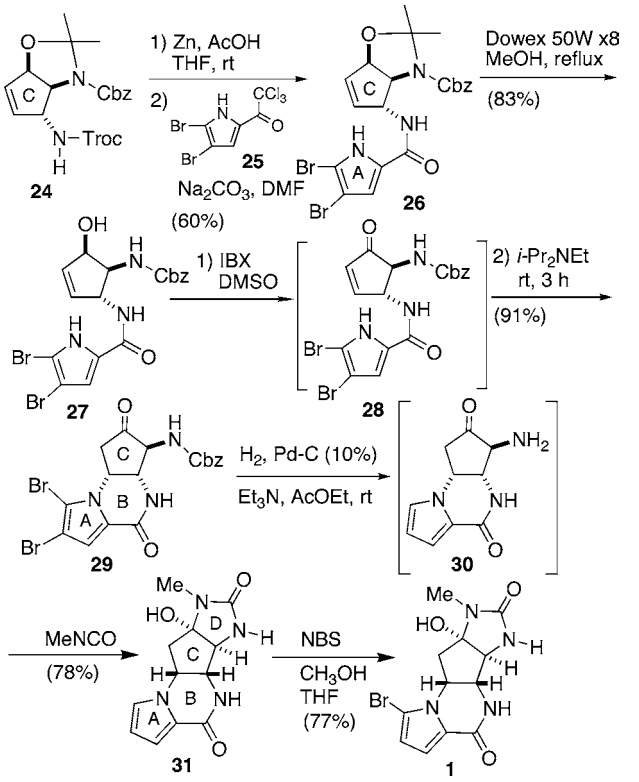


(22) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, 2039. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1988**, 4413.

rivatization of isocyanate **23**. As a result, the trichloroethoxy (Troc) carbamate **24** was obtained in 95% yield.

With our C-ring intermediate available, we next attempted B-ring construction (Scheme 5). At this stage, we planned

Scheme 5. Completion of the Total Synthesis of Agelastatin A



to introduce two electron-withdrawing bromines onto the pyrrole ring-A as in **25**, analogously to Hale et al: this tactic would lower the pK_a of the pyrrole nitrogen and circumvent the isomerization problem of a labile cyclopentenone such as **28** during the base-catalyzed intramolecular Michael addition.[23] Annulation of ring-B onto the cyclopentene C-ring intermediate **24** began with removal of the Troc-group with zinc. The resultant amine was treated with bromopyrrole **25** and sodium carbonate in DMF to afford the amide **26**.[24] Deprotection of the acetonide group in **26** with Dowex 50W × 8 in methanol at reflux furnished the allyl alcohol **27**. Although IBX oxidation of **27** was successful, the resultant cyclopentanone **28** was found to be rather labile. Since *tert*-amine was reported to be compatible with IBX oxidation,[25] a one-flask two-sequence protocol was secured. Allyl alcohol **27** was thus initially treated with IBX in DMSO. After checking the consumption of **27** by TLC, Hünig base was added to the reaction mixture. Pleasingly, an intramolecular conjugate addition reaction occurred smoothly at ambient temperature for 3.5 h to deliver the desired ABC-tricyclic ring system **29** in 91% yield.

The final stage of D-ring construction started with deprotection of the Cbz group and concomitant hydrogenolysis of the two bromine substituents in the pyrrole ring-A; thus, **29** was treated with hydrogen and a catalytic amount of 10% palladium on carbon in the presence of triethylamine. Without isolation of **30**, the reaction mixture was treated with methyl isocyanate[26] to provide the cyclic hemiaminal; debromoagelastatin A (**31**) was isolated in 78% yield for these three steps.

Following the protocol of Feldman, regioselective bromination of **31** with NBS in a 1:2 mixture of MeOH/THF furnished (−)-agelastatin A (**1**) in 77% yield. The ^{1}H and ^{13}C NMR spectra of our synthetic sample matched those reported by the previous syntheses.

Thus the total synthesis of the marine alkaloid (−)-agelastatin A (**1**) has been accomplished starting from L-arabitol **10**. The vicinal diamine moiety was successfully installed within the intermediate **24** via [3.3] sigmatropic rearrangements of allyl cyanates, and the central cyclopentane ring-C was efficiently constructed by RCM using a highly functionalized 1,5-diene **8** as a substrate.

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

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(23) Similar strategy using bromopyrrole was noted in the previous synthesis of Hale, which was rationalized and modified in our route. Hale, K. J.; Domostoj, M. M.; El-Tanami, M.; Campbell, F. C.; Mason, C. K. Total Synthesis and Mechanism of Action Studies on the Antitumor Alkaloid, (−)-agelastatin A. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Elsevier: 2005; pp 352−394. See also ref 10b and Supporting Information.

(24) (a) Belanger, P. *Tetrahedron Lett.* **1979**, *20*, 2505. (b) Lindel, T.; Hochgürtel, M. *J. Org. Chem.* **2000**, *65*, 2806.

(25) (a) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272. (b) Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485.

(26) Commercially available methyl isocyanate was dissolved in THF and then used as a THF-solution, which was titrated by the reaction with excess benzylamine and isolation of the produced methyl benzyl urea. We thank Prof. Weinreb, Dr. Stien, and Prof. Davis for informing us of the source of methyl isocyanate (see ref 8a and 11).