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Total Synthesis of (+)-Brasilenyne. Application of an Intramolecular Silicon-Assisted Cross-Coupling Reaction

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Abstract: The first enantioselective total synthesis of (+)-brasilenyne (**1**) has been achieved in 19 linear steps, with 5.1% overall yield from L-(*S*)-malic acid. The construction of the oxonin core containing a 1,3-*cis*,*cis* diene unit was accomplished with a tandem ring-closing metathesis/silicon-assisted intramolecular cross-coupling reaction. In addition, a key propargylic stereogenic center was created through a novel, highly diastereoselective ring opening of a 1,3-dioxolanone promoted by $TiCl_4$. This reaction proceeded through an oxocarbenium ion intermediate and the asymmetric induction was fully controlled by L-malic acid residue. The C(8) stereogenic center was set by a reagent-controlled asymmetric allylboration.

Introduction and Background

Red algae and marine organisms that feed on red algae, in particular *Laurencia* species, have produced various C_{15} nonterpenoid acetogenenins containing halogenated medium-ring ethers.[1] These metabolites contain a number of different ring sizes, such as those found in (+)-laurencin,[2] (+)-prelaureatin,[3] (+)-laurallene,[4] (−)-isolaurallene,[5] and (+)-obtusenyne[6] (Figure 1). Among them, (+)-brasilenyne (1), isolated from the digestive gland of a sea hare (*Aplysia brasiliana*) by Fenical et al.[7] in 1979, has a novel nine-membered cyclic ether skeleton containing a 1,3-*cis*,*cis*-diene unit. Because sea hares are incapable of evasive maneuvering, yet lack significant predators, it suggests that secondary metabolites, such as **1**, are produced and/or concentrated in the digestive gland to act as defensive chemicals. Indeed, the in vivo studies of **1** and (+)-*cis*-dihydrorhodophytin, a major component from same natural source, have been demonstrated to be potent antifeedants.[7a]

Biosynthetic investigations on cyclic ether metabolites of *Laurencia* species have demonstrated that lactoperoxidase (LPO) directly transforms 3*Z*,6*S*,7*S*-laurediol, which occurs in nature as various stereoisomers, into (+)-prelaureatin through a bromonium ion-induced ether formation.[8] Moreover, (+)-laurallene, (+)-laureatin, and (+)-isolaureatin are assumed to arise from (+)-prelaureatin by a similar biogenetic pathway.[3,9] Therefore,

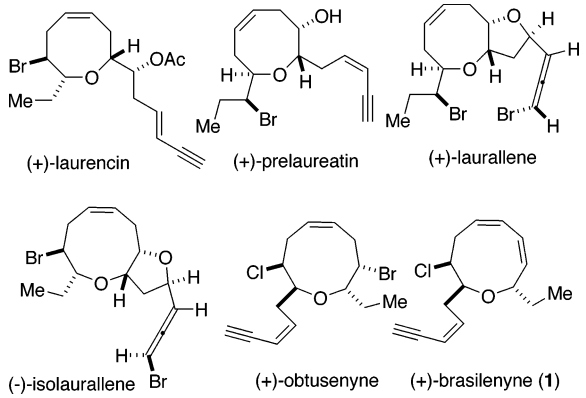

Figure 1. Representative C_{15} medium-sized ring ether marine metabolites.

the hypothetical intermediate, Cl-substituted laurediol, has been postulated to produce (+)-obtusenyne by a similar biotransformation, and further dehydrobromination affords (+)-brasilenyne.[7] The speculation was supported by the finding that those compounds have the same configuration at C(6) and C(7) of the Cl-substituted intermediate[10] (Scheme 1).

The interesting structure of these marine metabolites has stimulated a significant level of effort for the construction of oxonin and oxocene ring systems.[11] Recent representative examples include Crimmins' syntheses of (+)-prelaureatin[11b] and (+)-obtusenyne[11e] through an aldol or alkylation/ring-

(1) (a) Erickson, K. L. In *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1983; Vol. 5, pp 131−257. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1−49.
(2) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron Lett.* **1965**, *6*, 1091−1099.
(3) Fukuzawa, A.; Takasugi, Y.; Murai, A. *Tetrahedron Lett.* **1991**, *32*, 5597−5598.
(4) Fukuzawa, A.; Kurosawa, E. *Tetrahedron Lett.* **1979**, *20*, 2797−2800.
(5) Kurata, K.; Furusaki, A.; Suehiro, K.; Katayama, C.; Suzuki, T. *Chem. Lett.* **1982**, 1031−1034.
(6) (a) King, T. J.; Imre, S.; Oztunc, A.; Thomson, R. H. *Tetrahedron Lett.* **1979**, *20*, 1453−1454. (b) Howard, B. M.; Schulte, G. R.; Fenical, W. *Tetrahedron* **1980**, *36*, 1747−1751.
(7) (a) Kinnel, R. B.; Dieter, R. K.; Meinwald, J.; Engen, D. V.; Clardy, J. Eisner, T.; Stallard, M. O.; Fenical, W. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 3576−3579. (b) Fenical, W.; Sleeper, H. L.; Paul, V. J.; Stallard, M. O.; Sun, H. H. *Pure Appl. Chem.* **1979**, *51*, 1865−1874.
(8) (a) Ishihara, J.; Kanoh, N.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 737−740. (b) Fukuzawa, A.; Aye, M.; Nakamura, M.; Tamura, M.; Murai, A. *Chem. Lett.* **1990**, 1287−1290. (c) Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1972**, *13*, 2121−2124. For transformation of 3*E*,6*R*,7*R*-laurediol to deacetyl-laurencin by LPO, see: (d) Fukuzawa, A.; Aye, M.; Murai, A. *Chem. Lett.* **1990**, 1579−1580. (e) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193−4205.
(9) In vitro studies have shown that laureatin and isolaureatin were derived from *Z*-prelaureatin by LPO and laurallene was derived from *E*-prelaureatin by bromoperoxidase (BPO), see: Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371−8382.
(10) Norte, M.; Gonzalez, A. G.; Cataldo, F.; Rodriguez, M. L.; Brito, I. *Tetrahedron* **1991**, *47*, 9411−9418.

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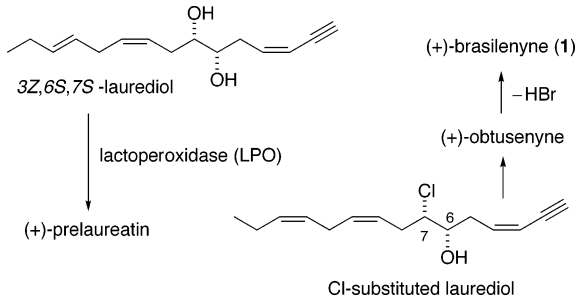
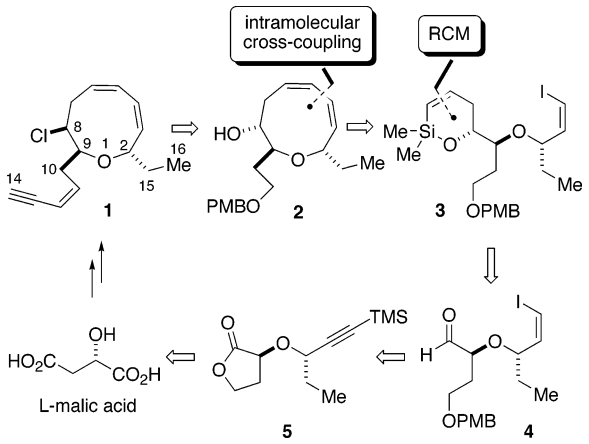
Scheme 1



closing metathesis (RCM) sequence, Overman's syntheses of (−)-laurenyne[11j] and (+)-laurencin[11k] by Lewis-acid-promoted alkene−acetal cyclization, and Holmes's synthesis of (+)-laurencin[11l] that features a Claisen rearrangement. These methods are particularly well suited for the construction of medium-ring ethers containing a *single* carbon−carbon double bond. The synthetic challenge of the oxonin core of **1**, however, requires the formation of a medium ring bearing a conjugated diene. Two recent reports from Negishi et al.[12] and Isobe et al.[13] describe viable methods for the synthesis of medium rings that contain a 1,3-diene. These reports feature the carbopalladation of an allene and the acid-catalyzed cyclization of an acetylene dicobalt complex.

As part of our program on the development of new silicon-based cross-coupling reactions, we have recently demonstrated the synthetic potential of the sequential ring-closing metathesis (RCM)/silicon-assisted intramolecular cross-coupling reaction for constructing medium-sized, carbo- and heterocyclic systems bearing a 1,3-*cis,cis*-diene unit.[14] This coupling process is ideally suited to generate the oxonin core of **1**, with its internal 1,3-diene. However, this approach introduces several challenges that require additional synthetic manipulations (Scheme 2). In contrast to the foregoing methodological studies on simpler systems, the side chain at C(9) and the ethyl group at C(2) presented potential difficulties for the intramolecular coupling process. In addition, the presence of the chlorine-bearing center at C(8) requires the creation of a hydroxyl functional group at C(8) of opposite configuration. This, in turn, allows the use of a temporary silicon tether for the construction a cyclic alkenylsilyl ether by RCM. The creation of the C(2) stereogenic center is the other critical part of the strategy needed for the synthesis of **1**. This problem stimulated the development of a new ring-opening reaction of a 1,3-dioxolanone with an acetylenic nucleophile to create the requisite stereogenic center at a propargylic position.

Scheme 2



The synthetic plan formulated for the synthesis of (+)-brasilenyne is outlined retrosynthetically in Scheme 2. Simplification of the enyne side chain and chloride functionality reduces the challenge to the intermediate **2**, which was projected to arise from a palladium-catalyzed, silicon-assisted intramolecular cross-coupling reaction of **3**. By use of the six-membered cyclic siloxane, the hydroxyl group liberated in the cross-coupling is perfectly situated for installation of the chloride at C(8). Cyclic alkenylsilyl ether **3** would arise from diastereoselective allylation of aldehyde **4** and application of ring-closing metathesis (RCM) of the vinyl alkenylsilyl ether derivative. The aldehyde **4** with a protected primary hydroxyl group, as well as the geometrically defined vinyl iodide could be, without difficulty, elaborated from **5**. The diastereo- and enantioselective synthesis of **5** represented an intriguing synthetic challenge, namely the construction of a doubly branched ether with flanking stereogenic centers (Scheme 3). The straightforward solution to this problem would involve a nucleophilic displacement reaction. Because both enantiomers of **6**[15] and **7**[16] are available, the doubly branched ether linkage can proceed in either direction. This approach was considered plausible, as both hydroxy groups are activated (flanked by carboxyl or alkynyl groups). However, in recognition of the difficulty of effecting displacements at sterically congested centers, an alternative approach featuring a diastereoselective ring opening of the 1,3-dioxolanone **8** was envisioned. This plan calls for the Lewis-acid-promoted addition of bis(trimethylsilyl)acetylene to the activated acetal.[17] Thus, the C(2) and C(8) stereocenters were to be installed through a reaction controlled by the stereocenter in the malic acid residue. Either approach is attractive, as both **6** and **8** could be easily derived from natural L-(*S*)-malic acid.

(11) For a review of construction of medium-ring ethers, see: (a) Elliott, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457−474. For total syntheses of (+)-prelaureatin, see: (b) Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473−5476. (c) Fujiwara, K.; Souma, S.-i.; Mishima, H.; Murai, A. *Synlett* **2002**, 1493−1495. For total syntheses of (+)-obtusenyne, see: (d) Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616−2617. (e) Crimmins, M. T.; Powell, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 7592−7595. For total syntheses of (−)-isolaurallene, see: (f) Crimmins, M. T.; Emmitte, K. A.; Choy, A. L. *Tetrahedron* **2002**, *58*, 1817−1834. (g) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533−1534. For total synthesis of (+)-laurallene, see: (h) Saitoh, T.; Suzuki, T.; Sugimoto, M.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 3175−3178. Also see ref 11b. For total synthesis of natural (+)-laurenyne, see: (i) Boeckman, R. K., Jr.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891−3894. For (−)-laurenyne, see: (j) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248−2256. For representative examples of total syntheses of (+)-laurencin, see: (k) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958−5966. (l) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483−7498. (m) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345−4348. (n) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029−2032. For total synthesis of (+)-isolaurepinnacin, see: (o) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 2446−2452.

(12) Ma, S.; Negishi, E.-i. *J. Am. Chem. Soc.* **1995**, *117*, 6345−6357.

(13) (a) Yenjai, C.; Isobe, M. *Tetrahedron* **1998**, *54*, 2509−2520. (b) Hosokawa, S.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 2609−2612. (c) Kira, K.; Isobe, M. *Tetrahedron Lett.* **2000**, *41*, 5951−5955.

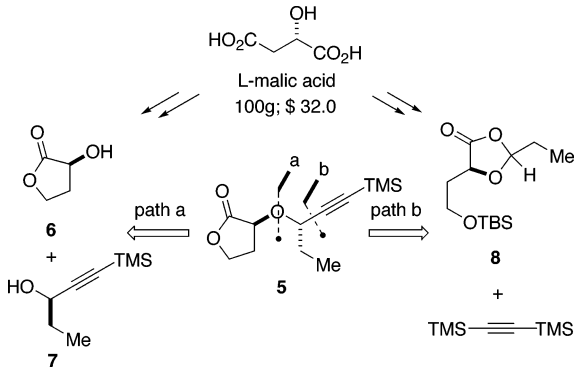
(14) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 2102−2103.

(15) For synthesis of **6**, see: (a) Green, D. L. C.; Kiddle, J. J.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2865−2874. (b) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129−9142. (c) Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000**, *65*, 7456−7467.

(16) For synthesis of **7**, see: (a) Allevi, P.; Ciuffreda, P.; Anastasia, M. *Tetrahedron: Asymmetry* **1997**, *8*, 93−99. (b) Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937−943. (c) Mukaiyama, T.; Suzuki, K. *Chem. Lett.* **1980**, 255−258. (d) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233−6236.

Therefore, the crucial components in this approach would be the sequential RCM/Pd-catalyzed, silicon-assisted intramolecular cross-coupling reaction for construction of the oxonin core structure, as well as the diastereoselective installation of a propargylic stereogenic center in key intermediate **5**. We describe herein the first total synthesis of (+)-brasilenyne by application of these new transformations as key strategic elements.[18]

Scheme 3

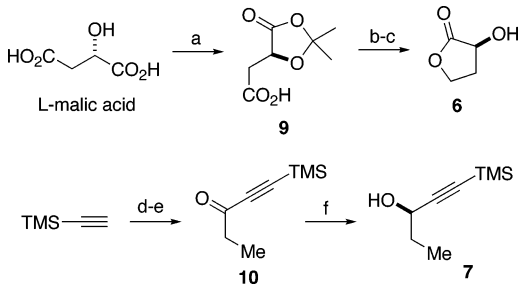


Results

Construction of the Ether Linkage. To evaluate the possibility to prepare the branched ether linkage by a direct displacement strategy, the enantiomerically pure alcohols **6** and **7** were prepared. The (*S*)-α-hydroxy-γ-butyrolactone **6** is commercially available but can also be easily prepared from L-(*S*)-malic acid in a three-step sequence in high chemical yield (Scheme 4).[15] Furthermore, highly enantiomerically enriched (98.8% ee) **7** was obtained in 95% yield by an efficient transfer hydrogenation reaction of the corresponding ketone **10** in *i*-PrOH with a catalytic amount of {[(1*R*,2*R*)-TsDPEN]RuCl(η^6-*p*-cymene)}, as developed by Noyori et al.[19] The enantiomeric purity of **7** was determined by CSP SFC analysis of the derived 3,5-dinitrobenzoate ester.

With both enantiomerically pure precursors in hand, the next objective was the union of **6** and **7** into intermediate **5**. An initial study on the activation of the propargylic hydroxyl group with Tf_2O, followed by displacement with **6**, was unsuccessful (Scheme 5). To identify the problem with this transformation, the stable mesylate **11** was prepared (by treatment of *rac*-**7** with MsCl and Et_3N) and then subjected to ether formation with **6** under various conditions. Unfortunately, no reaction occurred at all by using *i*-Pr_2NEt as the base. Both reactants, **6** and **7**, were stable under these, and even harsher, conditions (50−60 °C and/or neat). By employing K_2CO_3 or NaH as the base, silylated compound **12** and desilylated product **13** were observed

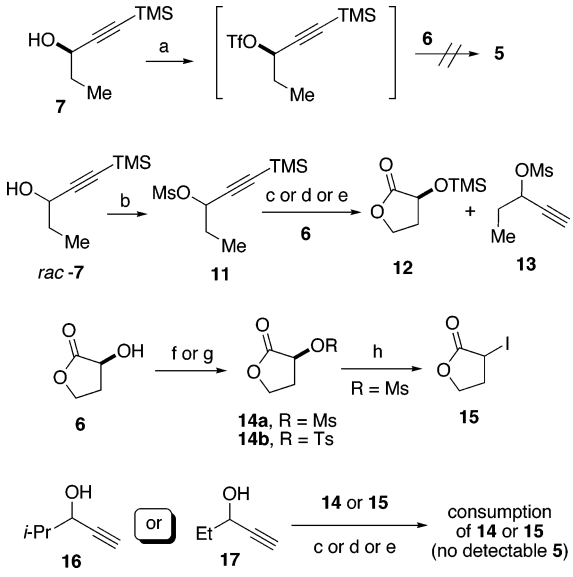
Scheme 4 [a]



[a] Reagents and conditions: (a) 2,2-methoxypropane, *p*-TSA·H_2O (1.0 mol %), room temperature, 3 h, 84%. (b) BH_3·THF, THF, 0 °C to room temperature, 12 h. (c) *p*-TSA·H_2O (1.0 mol %), benzene, 3 h, room temperature, 85% (two steps). (d) propanal, *n*-BuLi, THF, −70 °C to room temperature, 1 h, 94%. (e) PDC, 4Å MS, CH_2Cl_2, room temperature, 15 h, 85%. (f) {[(1*R*,2*R*)-TsDPEN]RuCl(η^6-*p*-cymene)} (0.5 mol %), *i*-PrOH, room temperature, 8 h, 95%.

by ^1H NMR analysis. Reversing the roles through activation of the hydroxyl group of **6** was another option. Activated substrates **14** and **15** were easily prepared from **6**. Treatment of compounds **14** or **15** with propargylic alcohols **16** or **17** using *i*-Pr_2NEt led to no reaction. By using K_2CO_3 or NaH as the base, complete consumption of **14** or **15** was observed, with no detectable amount of **5**.

Scheme 5 [a]



[a] Reagents and conditions: (a) Tf_2O, Et_3N, CH_2Cl_2, 0 °C to room temperature. (b) MsCl, Et_3N, CH_2Cl_2, −70 °C to room temperature, 30 min, 94%. (c) *i*-Pr_2NEt, $CDCl_3$ or neat, room temperature or 50−60 °C. (d) K_2CO_3, DMF, room temperature. (e) NaH, DMF, 0 °C to room temperature. (f) MsCl, Et_3N, CH_2Cl_2, −70 °C to room temperature, 15 min, 82%. (g) TsCl, Et_3N, cat. pyridine, room temperature, 2 h, 87%. (h) NaI, acetone, room temperature, 8 h, 85%.

Ring Opening of a 1,3-Dioxolanone. The failure to directly conjoin the two subunits **6** and **7** shifted the focus to the formation of a doubly branched ether **5** by the diastereoselective ring opening of a 1,3-dioxolanone. Asymmetric synthesis by ring opening of chiral acetal templates promoted by Lewis acids provides a route for selectively generating chiral *secondary* alcohols and/or ethers. Over the past two decades, many different nucleophilic organometallic reagents, as well as Lewis acids, have been successfully employed.[20] The diastereoselectivity of

(17) To the best of our knowledge, the ring opening of 1,3-dioxolanone with bis(trimethylsilyl)acetylene is unprecedented. Ring opening of acetal templates with silylacetylenic compounds promoted by Lewis acid have been reported, see: (a) Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904−2905. (b)Yamamoto, Y., Nishii, S.; Yamada, J.-i. *J. Am. Chem. Soc.* **1986**, *108*, 7116−7117. (c) Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648−7649.

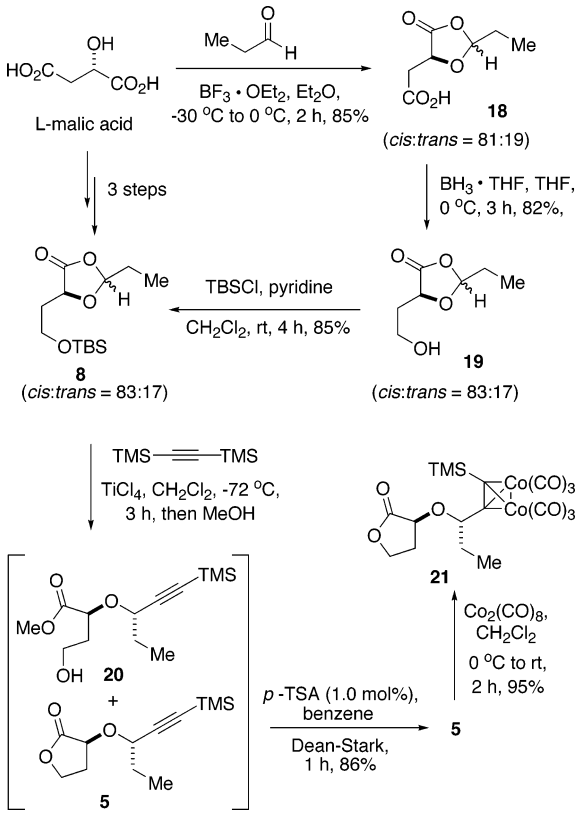
(18) Previous communication, see: Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196−15197.

(19) (a) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285−288. (b) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738−8739. The air-stable, purple Ru complex was easily prepared from (1*R*,2*R*)-1,2-diphenyl-*N*-(4-toluenesulfonyl)-ethylenediamine with $[RuCl_2(\eta^6$-*p*-cymene$)]_2$ in 87% yield.

this process strongly depends on the structure of the acetal, solvent, Lewis acid, as well as the nucleophilic reagent. Among them, acetylenic organometallic compounds have been employed as nucleophilic reagents to create a stereogenic center at propargylic positions with high diastereoselectivity.[17] In fact, ring opening of 1,3-dioxolanones with various nucleophilic reagents and Lewis acids has been extensively investigated.[21] However, the ring opening of a 1,3-dioxolanone with acetylenic organometallic reagents is unprecedented.

The 1,3-dioxolanone **8** was chosen to test this approach because (1) **8** can be rapidly obtained from the natural L-(*S*)-malic acid and (2) propanal can act both as the protecting group and as a part of the target compound **5** (Scheme 6). The

Scheme 6



synthesis of **8** began by the condensation of L-(*S*)-malic acid with propanal promoted by BF_3·Et_2O to afford the 1,3-dioxolanone **18** (85%) as an epimeric mixture slightly favoring the cis isomer (cis/trans = 81:19).[22] Selective reduction of the carboxylic acid using BH_3·THF at 0 °C provided **19** (82% yield) followed by protection of the primary alcohol thus formed with *tert*-butylchlorodimethylsilane, and pyridine afforded **8** in 85% yield (ca. 60−65% overall yield in three steps from L-(*S*)-malic acid). The poor selectivity in the preparation of the dioxolanone **18** was unexpected. On the basis of literature precedent, the construction of the 1,3-dioxolanone normally favors the more thermodynamically stable cis isomer with high diastereoselectivity.[22] Fortunately, this was subsequently shown to be inconsequential. Direct transformation of the cis/trans mixture of **18** to alcohol **19** and TBS ether **8** maintained the ratio (cis/trans = 83:17). The hydroxy 1,3-dioxolanone intermediate **19** was labile to both acid and bases, such as Et_3N, *i*-Pr_2NEt, imidazole, and *N*,*N*-(dimethylamino)pyridine, producing (*S*)-α-hydroxy-γ-butyrolactone **6**. However, by carrying out the reduction of **18** at 0 °C and protection of **19** using pyridine as the base, these transformations could be performed reproducibly on a large scale.

The Lewis-acid-mediated ring opening of **8** with bis(trimethylsilyl)acetylene employed $TiCl_4$ as the Lewis acid in a procedure similar to the ring opening of acetal templates developed by Johnson et al.[17a] Gratifyingly, ring opening of dioxolanone **8** proceeded smoothly to afford only two products after quenching with MeOH: the desired lactone **5** and the methyl ester **20**. Furthermore, treatment of the crude mixture with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene for 1 h gave **5** exclusively in 86% yield as a *single* diastereomer by ^1H NMR analysis. The *S* configuration of the propargylic position was further established by conversion of **5** to a dicobalt complex **21** with $Co_2(CO)_8$ in 95% yield. Slow sublimation of **21** at 65−68 °C (0.1 mmHg) gave deep red crystals, whose full stereostructure was confirmed by a single-crystal X-ray diffraction (Figure 2).[23]

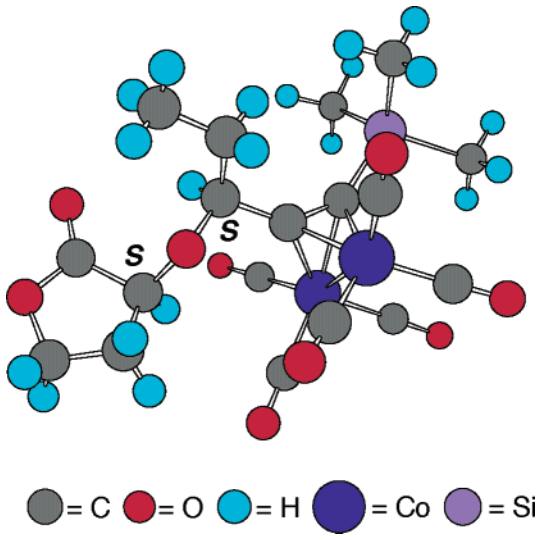


Figure 2. Chem3D image of X-ray crystal structure of cobalt complex **21**.

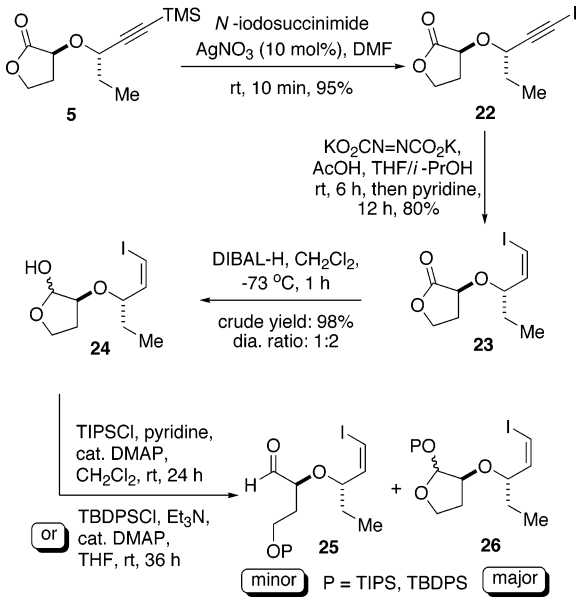
Implementation of the RCM/Cross-Coupling Sequence. To construct the oxonin core, the geometrically defined *Z*-vinyl iodide was next prepared for the key intramolecular cross-

(20) For some representative examples of ring opening of acetal templates, see: (a) Mori, A.; Ishihara, K.; Arai, I.; Yamamoto, H. *Tetrahedron* **1987**, *43*, 755−764. (b) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695−10704. (c) Lindell, S. D.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 3947−3950. (d) Harada, T.; Nakamura, T.; Kinugasa, M.; Oku, A. *J. Org. Chem.* **1999**, *64*, 7594−7600. (e) Bartlett, P. A. *J. Am. Chem. Soc.* **1983**, *105*, 2088−2089. (f) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294−2295. (g) For examples using acetylenic organometallic reagents, see ref 17. For mechanism studies, see: (h) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089−8110. (i) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485−6487. (j) Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475−3476. (k) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107−6115. (l) Sammakia, T.; Smith, R. S. *J. Org. Chem.* **1992**, *57*, 2997−3000.

(21) For some representative examples of ring opening of 1,3-dioxolanones, see: (a) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513−2516. (b) Heckmann, B.; Mioskowski, C.; Yu, J.; Flack, J. R. *Tetrahedron Lett.* **1992**, *33*, 5201−5204. (c) Heckmann, B.; Mioskowski, C.; Lumin, S.; Flack, J. R.; Wei, S.; Capdevila, J. H. *Tetrahedron Lett.* **1996**, *37*, 1425−1428. (d) Heckmann, B.; Mioskowski, C.; Bhatt, R. K.; Flack, J. R. *Tetrahedron Lett.* **1996**, *37*, 1421−1424.

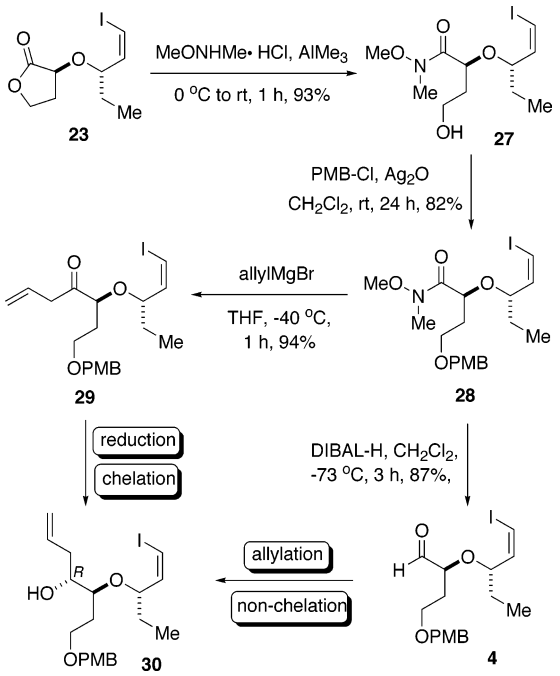
coupling reaction. Accordingly, the conversion of the trimethylsilyl group in **5** to alkynyl iodide **22** was efficiently accomplished by treatment of **5** with *N*-iodosuccinimide and a catalytic amount of silver nitrate in DMF (95% yield).[24] Furthermore, *cis*-reduction of **22** with diimide, generated in situ from potassium azodicarboxylate in AcOH/pyridine, gave the *Z*-alkenyl iodide **23** in 80% yield (Scheme 7).[25] The trace amount of over-reduction product can be removed by stirring the crude mixture in pyridine for 12 h at ambient temperature. Installation of the third stereogenic center (C(8)) calls for a diastereoselective allylation reaction of an aldehyde bearing a protected hydroxyl group, such as **25**. Thus, reduction of **23** with DIBAL-H afforded lactol **24** in good yield and in a 1:2 diastereomeric ratio. Unfortunately, all attempts to selectively protect the ring-opened hydroxy aldehyde intermediate with TIPSCl or TBDPSCl were unsuccessful. Only moderate conversion and a small amount of desired product **25** were obtained after a difficult separation from compound **26**.[26]

Scheme 7



Alternatively, the lactone **5** could be converted to the Weinreb amide **28**, which provided additional options for generation of the homoallylic alcohol **30**. For example, through the influence of an α-alkoxy group, homoallyl alcohol **30** could be obtained either by a chelation-controlled reduction of homoallyl ketone **29** or a nonchelation-controlled allylation of **4** (Scheme 8). Therefore, treatment of **23** with *N*,*O*-dimethylhydroamine hydrochloride salt in the presence of trimethylaluminum gave the amide **27** in 93% yield.[27] Further, protection of the hydroxyl

Scheme 8



group with *p*-methoxybenzyl chloride (PMBCl) under conditions that tolerate the vinyl iodide functionality (Ag_2O) afforded **28** in 82% yield.[28] Amide **28** could be converted to aldehyde **4** by reduction with DIBAL-H (87% yield)[29] or to homoallyl ketone **29** by treatment with allylmagnesium bromide (94% yield).[30]

With both precursors **4** and **29** in hand, the next critical stage was to introduce the third stereogenic center of **1**. Initial studies on reduction of homoallylic ketone of **29** into homoallyl alcohol **30** are compiled in Table 1. The use of DIBAL-H as the reducing agent (to tolerate the vinyl iodide functionality) gave an excellent chemical yield (Table 1, entry 1), but with unsatisfactory diastereoselectivity, slightly favoring the undesired *S* isomer. All attempts to improve the selectivity by employing $MgBr_2$ and ZnI_2 were fruitless (entries 2 and 3).[31] The LS-Selectride led to formation of the undesired *S* isomer (entry 4).

Table 1. Reduction of Homoallyl Ketone **29**

entry	conditions	**30** yield, % (ratio; *S*/*R*)[a]
1	DIBAL-H, THF, −73 °C	93 (57:43)
2	DIBAL-H, $MgBr_2$, CH_2Cl_2, −73 °C	94 (60:40)
3	DIBAL-H, ZnI_2, CH_2Cl_2, −75 °C	92 (52:48)
4	LS-Selectride, THF, −72 °C	− (ca. 85:15)[b]

[a] Number was corresponding to isolated yield and the ratio was determined by ^{1}H NMR integration. [b] Product contained small amount of residue from the reducing agent.

Next, the influence of the α-alkoxy group on the selective allylation of **4** by non-chelation-controlled addition was assayed

(22) (a) Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1992**, *57*, 3380−3387. (b) Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *38*, 8781−8784.
(23) The crystallographic coordinates of the dicobalt complex have been deposited with the Cambridge Crystallographic Data Centre, deposition no. CCDC-195245.
(24) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485−486.
(25) For modified procedures, see: (a) Nicolaou, K. C.; Marron, B. E.; Veale, C. A.; Webber, S. E.; Serhan, C. N. *J. Org. Chem.* **1989**, *54*, 5527−5535. (b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667−3670.
(26) (a) Kazuta, Y.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2002**, *67*, 1669−1677. (b)Yau, E. K.; Coward, J. K. *J. Org. Chem.* **1990**, *55*, 3147−3158.
(27) A modified procedure, see: Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74−79.
(28) Bouzide, A.; Sauve, G. *Tetrahedron Lett.* **1997**, *38*, 5945−5948.
(29) For modified procedures, see: (a) Wernic, D.; DiMaio, J.; Adams, J. *J. Org. Chem.* **1989**, *54*, 4224−4228. (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467.
(30) For modified procedures, see: (a) Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron* **1995**, *51*, 10343−10360. (b) Berts, W. B.; Luthman, K. *Tetrahedron* **1999**, *55*, 13819−13830.
(31) (a) For using $MgBr_2$, see ref 30a. (b) For using ZnI_2, see: Solladie, G.; Hanquet, G.; Rolland, C. *Tetrahedron Lett.* **1999**, *40*, 177−180.

(Table 2). By using allyltrimethylsilane as the allylating reagent and $BF_3{\cdot}Et_2O$ as the Lewis acid, only a 26:74 (*S*/*R*) ratio of alcohol **30** was obtained in 78% isolated yield, favoring the desired *R* isomer (Table 2, entry 1). Increasing the amount of Lewis acid (4.0 equiv) did not have a significant effect on either the yield or the selectivity (entry 2).[32] Allyltributyltin was also employed as the allylation reagent,[33] but poor selectivity was obtained with this reagents as well (entry 3). Direct addition with allylmagnesium bromide in the presence of $ZnCl_2$ gave **30** in a 91% yield as a ca. 1:1 mixture of diastereomers (entry 4).[34]

Table 2. Allylation of Aldehyde **4**

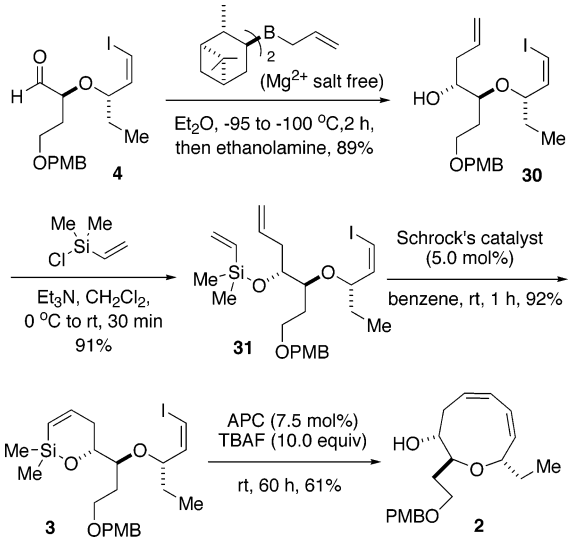
entry	conditions	**30** yield, % (*S*/*R*)[a]
1	allylSiMe$_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −73 °C	78 (26:74)[b]
2	allylSiMe$_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −73 °C	73 (27:73)[c]
3	allylSnBu$_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, −74 °C	87 (38:62)[d]
4	allylMgBr, $ZnCl_2$, Et_2O, −78 °C	91 (49:51)[e]
5	allylB((−)-Ipc)$_2$, Et_2O, −74 °C	72 (7:93)

[a] Yield of isolated product; the ratio was determined by ^{1}H NMR integration. [b] AllylSiMe$_3$ (2.0 equiv) and $BF_3{\cdot}Et_2O$ (2.0 equiv) were employed. [c] AllylSiMe$_3$ (2.5 equiv) and $BF_3{\cdot}Et_2O$ (4.0 equiv) were employed. [d] AllylSnMe$_3$ (2.0 equiv) and $BF_3{\cdot}Et_2O$ (2.0 equiv) were employed. [e] AllylMgBr (1.5 equiv) and $ZnCl_2$ (1.75 equiv) were employed.

The successful generation of **30** was eventually achieved by employing the chiral allylborane reagent, allylB((−)-Ipc)$_2$, developed by Brown et al.[35] Treatment of **4** with the reagent generated in situ from (+)-B-chlorodiisopinocampheylborane [(+)-DIP-Cl] and allylmagnesium bromide afforded **30** in 72% yield with a 93:7 diastereoselectivity (entry 5). This reagent has been shown to exhibit a strong intrinsic selectivity bias. Thus, the allylation with allylB((−)-Ipc)$_2$, derived from (−)-α-pinene, should give the corresponding *R* configuration at the homoallylic position.[35]

A significant improvement in yield (89%) and selectivity (>97:3) in the allylation was obtained under Mg^{2+}-salt free conditions at −100 °C (Scheme 9).[35b] Subsequent silylation of the secondary alcohol with chlorodimethylvinylsilane provided vinyl silyl ether **31** in 91% yield. This silylvinyl ether was subjected to the RCM reaction using Schrock's molybdenum complex [(CF$_3$)$_2$MeCO]$_2$Mo(=CHCMe$_2$Ph)(=NC$_6$H$_3$-2,6-*i*-Pr$_2$) as the catalyst.[36] By using a 5.0 mol % catalyst loading in benzene at room temperature, the ring closure went to completion efficiently within 1 h to afford **3** in excellent yield (92%). The crucial intramolecular cross-coupling reaction of **3** was carried out under the optimized conditions established previously: 7.5 mol % of [allylPdCl]$_2$ as the catalyst and 10 equiv of 1.0 M TBAF solution as the activator using a syringe-pump addition.[14] The reaction proceeded smoothly to afford the corresponding nine-membered ether **2** in 61% yield. Surprisingly, no significant influence by either the bulky side chain or the ethyl group was observed.

Scheme 9

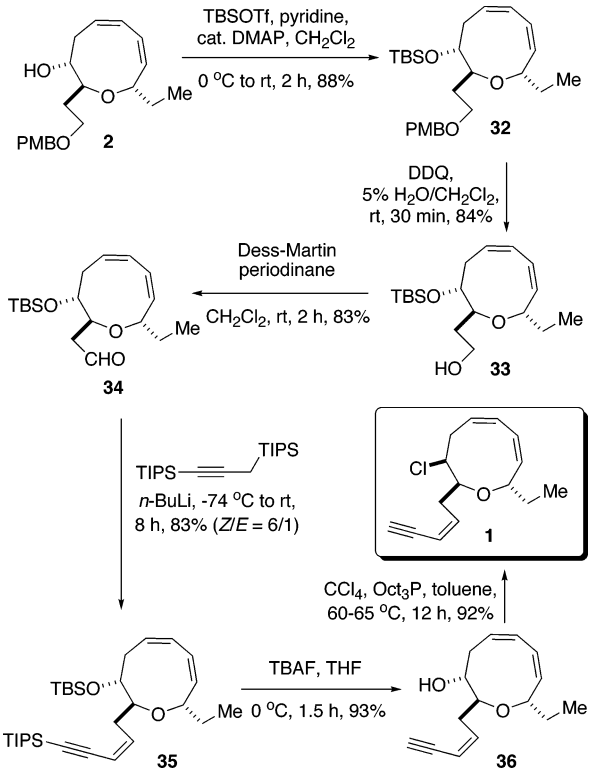


Completion of the Synthesis of 1. The completion of the total synthesis of **1** required transformation of the enyne side chain as well as introduction of the chloride functionality (Scheme 10). To avoid the potential elimination of hydrochloride, the installation of the chloride was chosen to be the final step. Elaboration of the enyne side chain began by protection of the hydroxyl group with TBSOTf using pyridine and a catalytic amount of DMAP to afford **32** in 88% yield. Deprotection of the PMB group with DDQ in CH_2Cl_2/H_2O (19/1)[37] gave **33** efficiently in 84% yield. Oxidation of **33** with Dess−Martin periodinane[38] afforded aldehyde **34** in 83% yield (61% overall yield from coupling product **2**). Peterson-type olefination as described by Corey et al.[39] was employed to introduce the required *Z*-enyne side chain. Thus, treatment of **34** with lithiated 1,3-bis(triisopropyl)propyne at low temperature, followed by slow warming of the mixture to room temperature, produced the enyne product **35** in 83% yield with ca. 6:1 *Z*/*E* geometric selectivity. Attempts to improve the geometric selectivity by employment of $MgBr_2$ led to failure. Mainly, elimination of the β-alkoxy group forming an α,β-unsaturated aldehyde was observed by ^{1}H NMR analysis [characteristic signals: 9.55 (d, J = 8.0, 1H, CHO); 6.78 (dd, J = 15.5, 4.5, 1 H, Hβ); 6.27 (dd, J = 16.0, 8.0, 1 H, Hα)].[40] Subsequently, deprotection of the TBS group, as well as the TIPS group, with a 1.0 M TBAF solution in THF afforded hydroxy enyne **36** in 93% yield. Finally, inversion of the 8*R* hydroxyl group into the 8*S* chloride using CCl_4/(*n*-Oct)$_3$P in toluene[11m] at 60−65 °C completed the first total synthesis of (+)-brasilenyne (**1**). The physical and spectroscopic data for the synthetic sample were nearly identical in all respects [mp 37−38 °C (lit. 36−37 °C), ^{1}H NMR, ^{13}C

(32) (a) Danishefsky, S. J.; Deninno, M. P.; Phillips, G. B.; Zelle, R. E. *Tetrahedron* **1986**, *42*, 2809−2819. (b) Veloo, R. A.; Wanner, M. J.; Koomen, G.-J. *Tetrahedron* **1992**, *48*, 5301−5316.
(33) Heck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265−268.
(34) Scarlato, G. R.; DeMattei, J. A.; Chong, L. S.; Ogawa, A. K.; Lin, M. R.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 6139−6152.
(35) (a) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570−1576. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404.
(36) The Schrock molybdenum complex is commercially available (Strem) and can be prepared according to the reported procedure with consistent purity and reactivity, see: (a) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287−2289. (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886. (c) Oskam, J. H.; Fox, H. H.; Yap, K. B.; McConville, D. H.; O'Dell, R.; Lichtenstein, B. J.; Schrock, R. R. *J. Organomet. Chem.* **1993**, *459*, 185−198. (d) Fox, H. H.; Lee, J.-K.; Park, L. Y.; Schrock, R. R. *Organometallics* **1993**, *12*, 759−768.
(37) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021−3028.
(38) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(39) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719−722.
(40) Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568−5570.

NMR, IR, and $[\alpha]^{24}_D$ +228.0 (c = 1.08, $CHCl_3$)]; lit. +216 (c = 0.017, $CHCl_3$) to those reported for natural (+)-brasilenyne.[7a]

Scheme 10



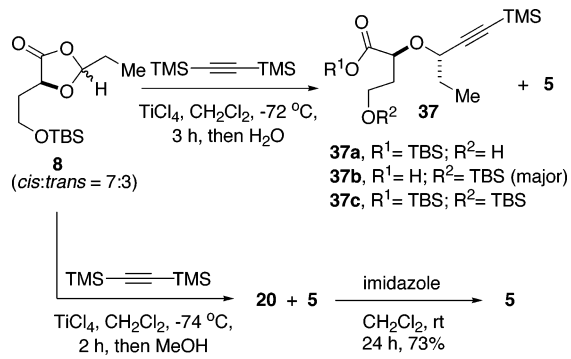
Discussion

Although the synthesis of (+)-brasilenyne was undertaken to test the applicability of the tandem RCM/silicon-directed cross-coupling to a challenging synthetic target, this transformation proceeded, happily, without difficulty. On the basis of prior studies in these laboratories, the conditions optimized for each of the two reactions could be directly applied to the more-complex substrate **31** with excellent results. Therefore, the key strategic maneuver shall occasion only minor comment, and, instead, relinquish the spotlight to the supporting players assigned to create the stereogenic centers in (+)-brasilenyne.

Formation of Intermediate 5. The failure to create a doubly branched ether by classic substitution reactions necessitated the development of an alternative strategy that could control the introduction of the propargylic center from a preexisting enantiopure material. The diastereoselective opening of a malic-acid-derived 1,3-dioxolanone offered an attractive solution.

In initial studies on the Lewis-acid-promoted ring opening of **8** with bis(trimethylsilyl)acetylene, TMSOTf was found to be unsuitable for this reaction, giving complex mixtures along with deprotection of the dioxolanone. Titanium tetrachloride was the most effective promoter. Moreover, the workup procedure greatly influenced the product distribution. For example, direct aqueous workup produced several components, such **37a**−**c** and **5** with **37b** as major product, whereas **20** and **5** were obtained after quenching with methanol (Scheme 11). Notably, each component comprised only a single diastereomer, indicating that the ring-opening process was highly diastereoselective. The conversion of **20** to the desired lactone was easily achieved by treatment with imidazole in CH_2Cl_2 to afford **5** in 73% yield after 24 h. However, using a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene gave **5** more efficiently.

Scheme 11



Diastereoselectivity of Ring Opening of 8. The ring opening of acetal templates, with weakly nucleophilic acetylenic reagents, such as bis(trimethylsilyl)acetylene, presumably react in the S_N1 region of the mechanistic continuum (i.e., by Lewis-acid-assisted ring opening prior to nucleophilic attack).[20h] In these cases, the asymmetric induction was rationalized by invoking Cram's rule as applied to the oxocarbenium ion intermediate.[17b] Indeed, the fact that a single diastereomer **5** was obtained from a cis/trans mixture of **8** strongly indicated that (1) the mechanism of ring opening of the 1,3-dioxolanone also proceeded through an oxocarbenium ion intermediate and (2) the high diastereoselectivity was fully controlled by the stereogenic center of the L-(*S*)-malic acid residue.[21a] It is worth noting that the more-labile C−OCO bond in the 1,3-dioxolanone can facilitate the formation of the reactive oxocarbenium ion intermediate, particularly in the presence of a strong Lewis acid such as $TiCl_4$.

A rationale for the convergent diastereoselectivity is formulated in Figure 3. The equilibration of intermediates **A** and **B** could presumably be achieved easily in the presence of a strong Lewis acid.[21a] To minimize dipole−dipole repulsion, oxocarbenium ion and Ti-coordinated carboxylate are arranged in an antiperiplanar conformation. In addition, the ring-opened *E*-oxocarbenium ion **A** is proposed to be thermodynamically favored. This is due to the reduced steric interaction between the malic acid residue and the ethyl group. Furthermore, nucleophilic attack from the *Re*-face avoids significant steric repulsion from the bulky R group (CH_2CH_2OTBS), thus affording the desired diastereomer **5**.

Allylboration of Aldehyde 4. The inability to accomplish substrate-controlled diastereoselectivity in the nucleophilic addition of hydrides to ketone **29** or organometallic reagents to aldehyde **4** prompted the use of Brown's allylB((−)-Ipc)$_2$ reagent, which exhibits an overwhelming intrinsic bias.[35] The highest yield (89%) and diastereoselectivity (>97:3) was achieved under a magnesium-salt-free condition at −100 °C (Scheme 9).[35b] In the presence of magnesium salt, the allylboration proceeded less efficiently, presumably due to the formation of a stable borate-magnesium complex, which can slow the rate of allylboration. On the basis of much literature precedent, allylB((−)-Ipc)$_2$ prepared from (+)-B-chlorodiisopinocampheylborane should produce the *R*-configuration at the homoallyl position.[35a] To confirm this stereochemical outcome, the allylboration product **30** was elaborated to lactone **39**, which could be structurally correlated to the known compounds,

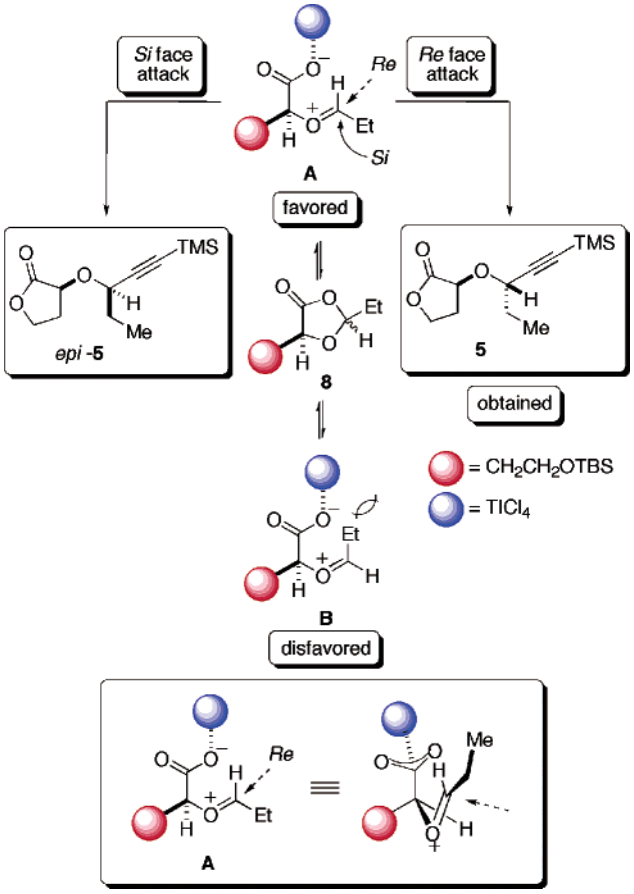


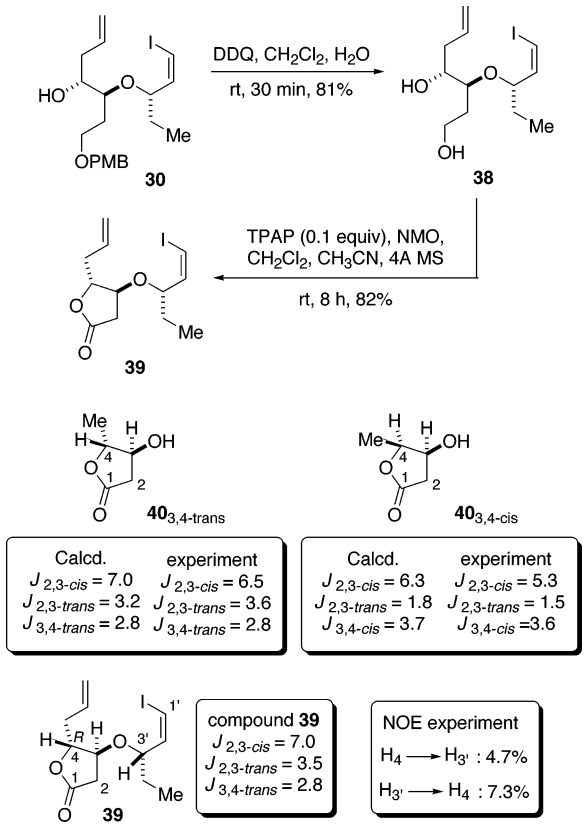
Figure 3. Proposed mechanism of ring opening of 1,3-dioxolanone **8**.

40$_{3,4-trans}$ and **40**$_{3,4-cis}$ (Scheme 12).[41] Treatment of **30** with DDQ in CH_2Cl_2/H_2O (19/1) gave diol **38** in 81% yield. Subsequent oxidation was carried out with a catalytic amount of tetrapropylammonium perruthenate and *N*-methylmorpholine-*N*-oxide to furnish lactone **39** in 82% yield.[42] In the ^{1}H NMR spectra of **39**, the coupling constants $J_{2,3-cis}$, $J_{2,3-trans}$, and $J_{3,4-trans}$ are 7.0, 3.5, and 2.8 Hz, respectively. These data are well matched to those calculated (7.0, 3.2, and 2.8 Hz) and experimentally determined (6.5, 3.6, 2.8 Hz) for **40**$_{3,4-trans}$. Importantly, strong NOE enhancements between HC(4) and HC(3′) were also observed. A 4.7% enhancement of HC(3′) was observed when HC(4) was irradiated, whereas a 7.4% enhancement of HC(4) was observed. These results strongly suggest that HC(4) and the alkenyl iodide residue exist in a cis-relationship, which therefore further supports the expectation that the *R* configuration was obtained in the asymmetric allylboration reaction.

Synthesis of 1. Despite the difficulty of creating the doubly branched ether linkage from **6** and **7**, several subsequent transformations did benefit from this sterically congested subunit. For instance, the branched ether at the propargylic position of **22** (C(2) of **1**) suppressed the over-reduction of the acetylene group with diimide (Scheme 7).[25] The desired product **23** was obtained in good yield (80%), with only a trace amount of over-reduction product. By contrast, the presence of a simple

(41) Jaime, C.; Segura, C.; Dinares, I.; Font, J. *J. Org. Chem.* **1993**, *58*, 154−158.
(42) (a) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666. (b) Burke, S. D.; Austad, B. C.; Hart, A. C. *J. Org. Chem.* **1998**, *63*, 6770−6771.

Scheme 12



methylene group at the propargylic position gave rise to a substantial amount of the over-reduction product, typically ca. 20−30%.[14] Furthermore, the branched ether flanking the vinyldimethylsilyl subunit of **31** (C(9) of **1**) provided an important conformational constraint that facilitated the RCM process. The cyclic alkenylsilyl ether **3** was obtained in excellent yield (92%) within 1 h, using only 5 mol % of Schrock's catalyst (Scheme 9). In previously reported methodological investigations, substrates bearing a simple methylene group in this position required a higher catalyst loading (8.0 mol %) and a longer reaction time (9−24 h) to reach completion.[14] Fortunately, the intramolecular cross-coupling reaction in the formation of the oxonin core was only minimally influenced by the steric hindrance of branched ether as established in model studies.[14]

The completion of the synthesis from coupling product **2** focused on the introduction of the enyne side chain and the chloride function. To achieve high geometric selectivity, the lithiated reagent from 1,3-bis(triisopropylsilyl)propyne was employed for Peterson-type olefination, as described by Corey et al.[39] However, only moderate geometric selectivity (ca. *Z*/*E*, 6/1) was obtained in the case of **34** (Scheme 10). Attempts to increase the geometric selectivity by the use of magnesium bromide, as described by Yamamoto et al.,[40] were unsuccessful. The coordination of the β-alkoxy group with Mg^{2+} apparently facilitated the elimination process, producing an α,β-unsaturated aldehyde. Additionally, an oft-used two-step sequence, which features the Stork−Wittig reaction to generate a *Z*-alkenyl iodide, followed by Sonogashira coupling,[11b,e] provided similar yields and selectivities to the Petersen protocol. Finally, the installation of (8*S*)-Cl was effected using the $CCl_4/(n\text{-Oct})_3P$ combination, as described by Murai et al.[11m] The high yield (92%) obtained in this case was particularly satisfying, as

significantly lower yields (ca. 60−75%) have been observed, in eight- and nine-membered-ring unsaturated ethers, apparently from competitive dehydration.[11e,i]

Conclusion

The first total synthesis of (+)-brasilenyne has been accomplished in a linear approach (19 steps, 5.1%) from commercially available L-(*S*)-malic acid. The significant features of the strategy include (1) a highly diastereoselective ring-opening of 1,3-dioxolanone promoted by $TiCl_4$ for the novel creation of a propargylic stereogenic center and (2) the successful application of the sequential RCM/silicon-assisted intramolecular cross-coupling reaction for construction of a medium-sized ether ring with 1,3-*cis*,*cis*-diene unit. In addition, the reagent-controlled asymmetric allylboration was employed to generate a homoallyl alcohol with excellent diastereoselectivity, which is perfectly set for installation of the (*S*)-C(8)−Cl center. Further extension of this strategy to the construction of other medium-sized ring and macrocyclic compounds is underway.

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Supporting Information Available: Detailed procedures and full characterization of all synthetic intermediates and products are provided, along with spectral comparison of natural and synthetic (+)-brasilenyne. This material is available free of charge via the Internet at http://pubs.acs.org.

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