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Intramolecular Silicon-Assisted Cross-Coupling: Total Synthesis of (+)-Brasilenyne

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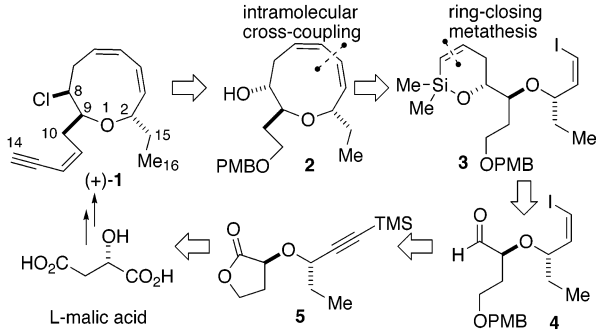
Red algae (and marine organisms that feed on red algae) of the *Laurencia* species produce a variety C_{15} acetogenenins containing halogenated medium-ring ethers.[1] Representative examples, such as (+)-laurencin and (+)-obtusenyne, have stimulated a significant level of effort for construction of oxocenes and oxonins.[2] (+)-Brasilenyne (**1**), an antifeedant isolated from sea hare (*Aplysia brasiliana*) by Fenical, et al. in 1979,[3] has a novel nine-membered cyclic ether skeleton containing a 1,3-*cis*,*cis*-diene unit which presents a formidable synthetic challenge.[4] A recent disclosure from these laboratories described the sequential ring-closing metathesis/silicon-assisted intramolecular cross-coupling for the construction of medium-sized, carbo- and heterocyclic rings bearing a 1,3-*cis*,*cis*-diene unit.[5] By applying this reaction as a key strategic element, we report herein the first, total synthesis of (+)-brasilenyne.

The retrosynthetic plan is outlined in Scheme 1. Simplification of the enyne side chain and chloride functionality in (+)-**1** reduces the challenge to the intermediate **2**, which was projected to arise from palladium-catalyzed, silicon-assisted intramolecular cross-coupling of **3**. The hydroxy group liberated in the cross-coupling is perfectly situated for installation of the chlorine. Alkenylsilyl ether **3** would arise from diastereoselective allylation of aldehyde **4** and application of ring-closing metathesis (RCM) of a vinyl alkenylsilyl ether derivative. The aldehyde **4** could be elaborated from **5** in which the propargylic stereogenic center would be set by the diastereoselective ring opening of a 1,3-dioxolanone, with bis(trimethylsilyl)acetylene. Thus, the C(2) and C(8) stereocenters were to be installed by reactions controlled by the C(9) center from malic acid.

Scheme 1



The synthesis of advanced intermediate **2** began by condensation of commercially available L-(*S*)-malic acid[6] with propanal promoted by $BF_3{\cdot}Et_2O$ to afford the 1,3-dioxolanone as a 7/3 mixture of cis and trans isomers (Scheme 2). Selective reduction of the carboxylic acid using $BH_3{\cdot}THF$ at 0 °C followed by protection of the primary alcohol with TBSCl and pyridine afforded **6** in 85% yield.[7] The stereogenic center at the propargylic position was introduced by Lewis-acid-mediated ring opening of **6** with bis(trimethylsilyl)-acetylene. Orienting experiments employed $TiCl_4$ as the Lewis acid by a procedure similar to the ring opening of acetal templates developed by Johnson, et al.[8a] Gratifyingly, ring opening of dioxolanone **6** proceeded smoothly to afford the desired compound **5** and ring-opened methyl ester of **5** (after quenching with MeOH). Furthermore, treatment of the crude mixture with a catalytic amount of *p*-TsOH in refluxing benzene gave **5** in 86% yield as a single diastereomer. The results strongly suggested that (1) the mechanism of ring opening of the dioxolanone proceeds through an oxocarbenium ion intermediate and (2) the high diastereoselectivity of the ring-opening process was controlled by the stereogenic center of the malic acid residue.[9,10]

Conversion of the trimethylsilyl alkyne to iodide **7** was efficiently accomplished by treatment of **5** with *N*-iodosuccinimide with a catalytic amount of silver nitrate in DMF.[11] Furthermore, cis reduction of **7** with potassium azodicarboxylate gave the geometrically defined *Z*-alkenyl iodide **8** in 80% yield.[12] Elaboration of **8** into aldehyde **4** began with the transformation of the lactone unit into a Weinreb amide.[13] Further protection of the hydroxy group with PMBCl afforded **9** in 82% yield.[14] Reduction of **9** with DIBAL-H at low temperature provided aldehyde **4** in 87% yield.

The next critical stage was to introduce the third stereogenic center of **1**. Diastereoselective allylation of **4** by a nonchelation-controlled addition afforded only a modest level of stereocontrol.[15] The successful generation of homoallylic alcohol **10** was ultimately achieved by employing a chiral allylborane reagent developed by Brown, et al.[16] Treatment of **4** with allyl$B(^{l}Ipc)_2$ generated in situ from (+)-*B*-chlorodiisopinocampheylborane afforded **10** in 72% yield with 93/7 diastereoselectivity. Furthermore, an improvement of yield (89%) and selectivity (>97/3) were secured by use of Mg^{2+} salt-free conditions at −100 °C.[16b]

With **10** in hand, the stage was set for implementation of the key RCM/cross-coupling sequence. Thus, silylation of **10** with chlorodimethylvinylsilane provided the vinyl silyl ether, which was subjected to the RCM reaction with Schrock's molybdenum complex as the catalyst.[17] By using 5.0 mol % of that catalyst, the ring-closure went to completion efficiently in 92% yield. The crucial nine-membered ring-forming reaction was carried out with 7.5 mol % of $[allylPdCl]_2$ as the catalyst and 10 equiv of TBAF as activator using syringe−pump addition.[5] The intramolecular cross-coupling proceeded smoothly to afford the corresponding nine-membered ether **2** in 61% yield.

Elaboration of the enyne side chain began by the protection of the hydroxy group with TBSOTf using pyridine and a catalytic amount of DMAP (88%). Further, deprotection of the PMB group

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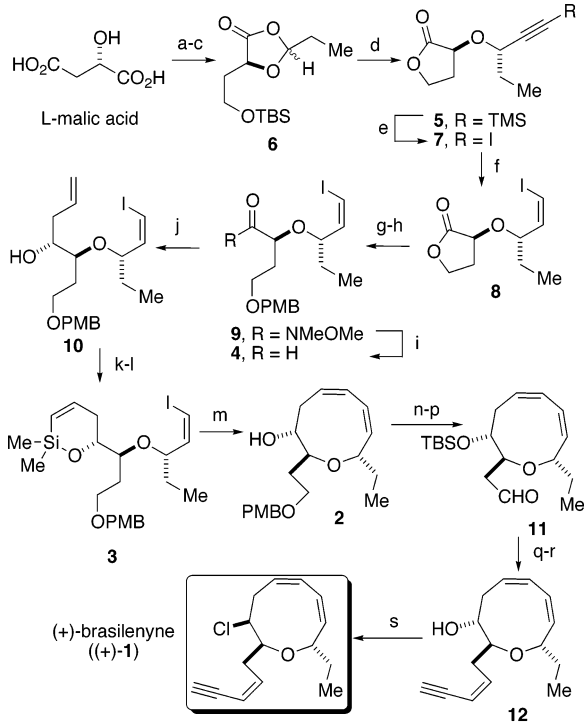
Scheme 2 [a]



[a] Conditions: (a) propanal, $BF_3{\cdot}Et_2O$, Et_2O, −30 °C to rt, 2 h, 85%; (b) $BH_3{\cdot}THF$, THF, 0 °C, 3 h, 82%; (c) TBSCl, pyridine, CH_2Cl_2, rt, 4 h, 85%; (d) (1) bis(trimethylsilyl)acetylene, $TiCl_4$, CH_2Cl_2, −73 °C, 3 h then (2) *p*-TSA (1 mol %), benzene, Dean−Stark, 1 h, 86%; (e) *N*-iodosuccinimide, $AgNO_3$ (10 mol %), DMF, rt, 10 min, 95%; (f) $KO_2CN{=}NCO_2K$, AcOH, THF/*i*-PrOH, rt, 6 h, 80%; (g) MeOMeNH·HCl, $AlMe_3$, CH_2Cl_2, 0 °C to rt, 1 h, 93%; (h) PMBCl, Ag_2O, CH_2Cl_2, rt, 24 h, 82%; (i) DIBAL-H, CH_2Cl_2, −73 °C, 3 h, 87%; (j) allylB(^{t}Ipc)$_2$, Et_2O, −100 °C, 2 h, 89%; (k) chlorodimethylvinylsilane, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min, 91%; (l) Schrock's catalyst (5 mol %), benzene, rt, 1 h, 92%; (m) $[allylPdCl]_2$ (7.5 mol %), TBAF, rt, 60 h, 61%. (n) TBSOTf, pyridine, DMAP (10 mol %), CH_2Cl_2, 0 °C to rt, 2 h, 88%; (o) DDQ, CH_2Cl_2/H_2O (19/1), rt, 30 min, 84%; (p) Dess−Martin periodinane, CH_2Cl_2, rt, 2 h, 83%; (q) 1,3-bis(triisopropylsilyl)propyne, *n*-BuLi, THF, −74 °C to rt, 8 h, 83% (*Z*/*E* = 6/1); (r) TBAF, THF, 0 °C, 1.5 h, 93%; (s) CCl_4, (*n*-Oct)$_3$P, toluene, 60−65 °C, 12 h, 92%.

with DDQ[18] followed by oxidation with Dess−Martin periodinane[19] afforded **11** in 61% overall yield from coupling product **2**. Peterson-type olefination[20] was employed to introduce the required *Z*-enyne side chain. Treatment of **11** with lithiated 1,3-bis(triisopropyl)-propyne at low temperature followed by slowly warming the solution to room temperature produced the enyne in 83% yield as a ca. 6/1 *Z*/*E* mixture of geometrical isomers. Subsequently, removal of the TBS as well as the TIPS groups with TBAF afforded the hydroxy enyne **12** in 93% yield. Finally, inversion of 8*R*-hydroxy group into the 8*S*-chloride using CCl_4/(*n*-Oct)$_3$P[2f] completed the total synthesis of (+)-brasilenyne **1**. The spectroscopic and analytical data from the synthetic sample were identical in all respects (mp, ^{1}H NMR, ^{13}C NMR, IR, and $[\alpha]^{24}_D$) to those reported for natural (+)-brasilenyne.

In conclusion, the first total synthesis of (+)-brasilenyne has been accomplished in 19 steps (5.1% overall) from L-(*S*)-malic acid. The synthesis features the sequential RCM/silicon-assisted intramolecular cross-coupling method for construction of a medium-sized ring ether bearing a 1,3-*cis*,*cis*-diene unit. Extension of this strategy to the synthesis of other medium-sized ring and macrocyclic compounds is under active study.

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Supporting Information Available: Detailed procedures and full characterization of all compounds along with ^{1}H and ^{13}C NMR and IR spectra of synthetic (+)-brasilenyne (PDF). X-ray crystallographic files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(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.
(2) (a) For a review of construction of medium-ring ethers, see: Elliott, M. C. *Contemp. Org. Synth.* **1994**, *1*, 457. (b) Hirama, M.; Rainder, J. D.; Eds. Synthesis of Marine Natural Products Containing Polycyclic Ethers. *Tetrahedron Symposium in Print No. 90* **2002,** *58*, 1779−2040. (c) Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. (+)-Obtusenyne. *J. Org. Chem.* **1999**, *64*, 2616. (d) For representative examples of total synthesis of (+)-laurencin, see: Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. (e) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483. (f) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345. (g) Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029. (h) Crimmins, M. T.; Emmitte, K. A. (−)-Isolaurallene. *J. Am. Chem. Soc.* **2001**, *123*, 1533.
(3) (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. (b) Fenical, W.; Sleeper, H. L.; Paul, V. J.; Stallard, M. O.; Sun, H. H. *Pure Appl. Chem.* **1979**, *51*, 1865.
(4) The parent 2,3,4,9-tetrahydrooxonin ring is unknown.
(5) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 2102.
(6) L-(*S*)-Malic acid was purchased from Aldrich and was shown to be of 99% ee by CSP-GLC analysis.
(7) All new compounds have been fully characterized, and all yields correspond to isolated, analytically pure materials. For detailed experimental procedures, see Supporting Information.
(8) To the best of our knowledge, the ring opening of a 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. (b) Yamamoto, Y., Nishii, S.; Yamada, J.-i. *J. Am. Chem. Soc.* **1986**, *108*, 7116. (c) Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648.
(9) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513.
(10) The *S*-configuration at the propargylic position was confirmed by conversion of **5** to a hexacarbonyldicobalt complex (with $Co_2(CO)_8$), whose full stereostructure was confirmed by single-crystal X-ray diffraction. The crystallographic coordinates of the cobalt complex have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC-195245.
(11) Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.
(12) 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. (b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667.
(13) For a modified procedure, see: Nemoto, H.; Nagamochi, M.; Ishibashi, H.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74.
(14) Bouzide, A.; Sauve, G. *Tetrahedron Lett.* **1997**, *38*, 5945.
(15) The diastereoselectivity of allylation of **4** with allyltrimethylsilane was only 74/26 when promoted by $BF_3{\cdot}Et_2O$, see: (a) Danishefsky, S. J.; Deninno, M. P.; Phillips, G. B.; Zelle, R. E. *Tetrahedron* **1986**, *42*, 2809. (b) For addition of allyltributylstannes to α-alkoxy aldehydes, see: Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265.
(16) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570. (b) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.
(17) Schrock's molybdenum complex is commercially available (Strem) or 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. (b) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875. (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. (d) Fox, H. H.; Lee, J.-K.; Park, L. Y.; Schrock, R. R. *Organometallics* **1993**, *12*, 759.
(18) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
(19) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(20) (a) Corey, E. J.; Rucker, C. *Tetrahedron Lett.* **1982**, *23*, 719. (b) See also Yamakado, Y.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 5568.

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