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Total Synthesis of Ryanodol

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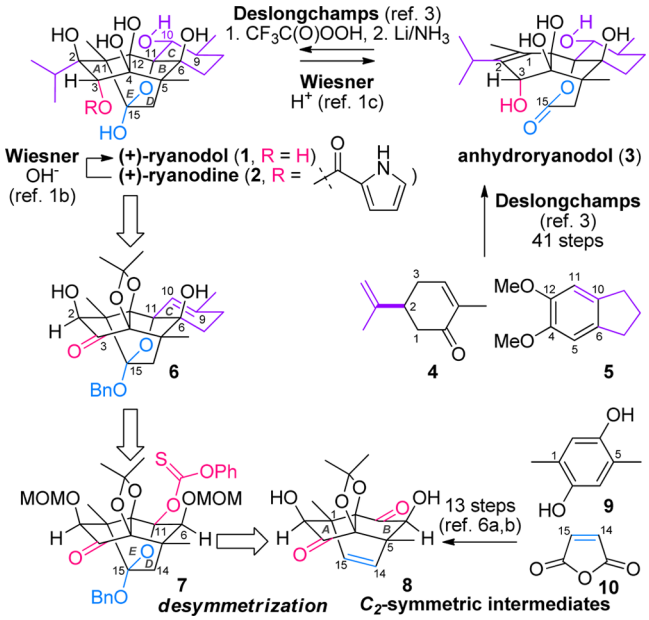
Supporting Information

ABSTRACT: Ryanodol (**1**) exists in nature in the form of the 1*H*-pyrrole-2-carboxylate ester derivative known as ryanodine, which is a potent modulator of the calcium release channel. The pentacyclic ABCDE-ring system of **1** is fabricated with eight oxy groups, three methyl groups, and one isopropyl group. All the eight tetrasubstituted stereocenters are concentrated within the 10-carbon ABDE framework. The total synthesis of this exceptionally complex molecule was achieved in 22 steps from the simple C_2-symmetric tricycle **8**. The synthetic route is based on installation of the seven stereogenic centers and formation of the four C−C bonds within the highly congested multicyclic format. The novel and flexible strategy developed here will enable the generation of chemical derivatives with different functional properties toward calcium release channels.

The South American plant *Ryania speciosa* has long been recognized for its insecticidal properties. Its active compound, an alkaloid known as ryanodine (**2**, Scheme 1),[1] alters the function of a high-conductance intracellular calcium channel known as the ryanodine receptor.[2] Since only a limited number of molecules have been reported to act by modifying the receptor, **2** and its derivatives are valuable tools for biological investigation of receptors and potential therapeutic agents for treating receptor-associated diseases.

A series of chemical degradation reactions of ryanodine (**2**) were discovered by Wiesner et al. during the course of their structural elucidation study.[1] The basic hydrolysis of **2** gave rise to the complex pentacyclic diterpenoid ryanodol (**1**) along with 1*H*-pyrrole-2-carboxylic acid. Further treatment of **1** under acidic conditions generated tetracyclic anhydroryanodol (**3**) through Grob-type fragmentation. On the other hand, the chemical assembly of ryanoids **1** and **2** has proven challenging: the de novo synthesis of **1** by Deslongchamps and co-workers in 1979 is the only successful synthesis reported to date, despite many attempts over the ensuing 30 years.[3,4] In their ingenious route, the degradation product **3** was constructed from (+)-carvone (**4**) and 5,6-dimethoxyindane (**5**) in 41 steps, and **3** was derivatized into **1** by C1-epoxidation and reductive C1−C15 bond formation. Herein, we describe the development of new methodologies and strategies for assembling the entire pentacycle of the ryanoids and the achievement of a second total synthesis of ryanodol (**1**). The present flexible route is highly suited for the generation of novel ryanoid derivatives with distinct biological activities.[5]

Scheme 1. Structure, Reactions, and Synthetic Plan of Ryanodol[a]



[a]C15-oxygen functionality, C3,C11-oxygen functionalities, and C2,C6,C11-carbon chains are colored in cyan, pink, and purple, respectively.

The complex molecular architecture of ryanodol (**1**) includes 5 rings, 11 contiguous stereogenic centers, and 8 oxygenated carbons (Scheme 1). The ABDE-ring moiety of **1** in particular heightens the synthetic challenge because all 8 tetrasubstituted carbons are concentrated within this 10-carbon framework. In our retrosynthesis, recognition of the embedded symmetric structure allowed the design of the significantly simplified C_2-symmetric tricycle **8** from the densely functionalized ABDE-ring of **1**. By taking advantage of its symmetric nature, the synthesis of (±)-**8** from **9** and **10** was previously realized in only 13 steps, including the installation of the four tetrasubstituted carbons (C1, C4, C5, and C12).[6] Therefore, the most critical issue for the total synthesis of **1** from **8** was to accommodate the remaining seven stereocenters in a highly congested format. We envisioned employing the α-alkoxy bridgehead radical reaction for stereospecific formation of the hindered C11-center from **7**, which would be prepared through

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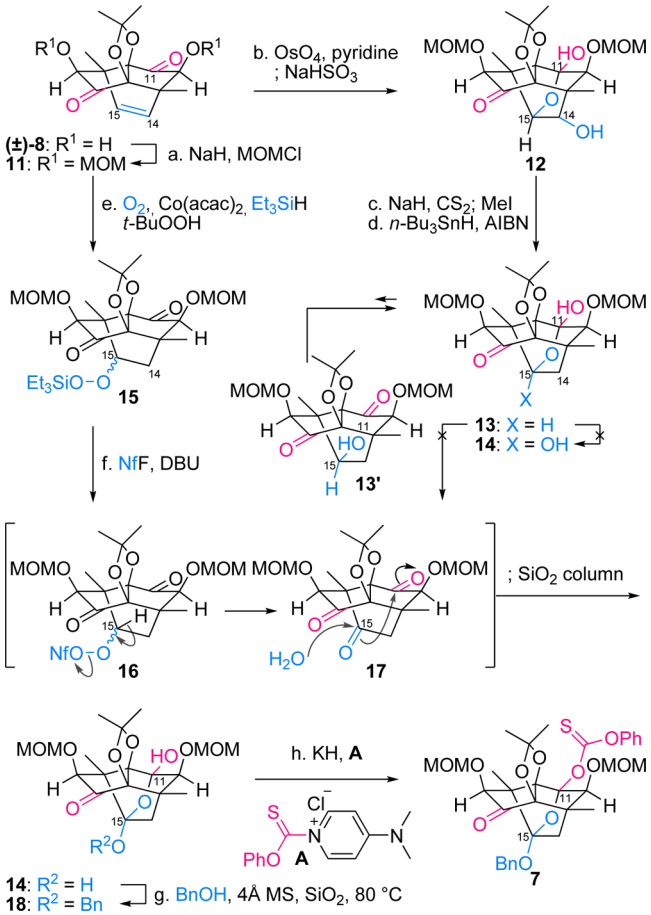
the oxidative desymmetrization of the C15-olefin of **8**. After radical bond formation from **7**, stereoselective C6-functionalization and C-ring formation would give the entire ring skeleton **6**, to which the four stereocenters (C2, C3, C9, and C10) would be stereoselectively introduced to construct the target structure **1**.

The newly designed strategy first necessitated desymmetrization of C_2-symmetric intermediate **8** by oxidation of the C15-olefin to the C15-ketone (Scheme 2). Before doing so, the two hydroxy groups of (±)-**8** were protected as their methoxymethyl (MOM)-ethers to yield **11**. Although the olefin was sterically surrounded by the AB-ring structure, introduction of the C15-oxygen functional group was attained via osmylation of the C14−C15 double bond of **11**, leading to diol **12**. The unnecessary C14-secondary alcohol of **12** was in turn removed via methyl xanthate formation and subsequent *n*-Bu_3SnH reduction to afford **13**.[7] Conversion of the thus-obtained hemiacetal **13** into triketone **17** or its hydrated derivative **14** was, however, unsuccessful under a variety of oxidation conditions. The extremely low concentration of the keto-alcohol form **13′** impeded its oxidation to **17**, while direct C15−H oxidation was not possible due to the presence of the more reactive C−H bonds in **13**.

Scheme 2. Development of the C15-Oxidation Protocol[a]



[a]Reagents and conditions: (a) NaH, MOMCl, *n*-Bu_4NI, THF, 92%; (b) OsO_4, pyridine; aq $NaHSO_3$, 85%; (c) NaH, CS_2, THF; MeI, 90%; (d) *n*-Bu_3SnH, 2,2′-azobis(isobutyronitrile) (AIBN), benzene, reflux, 86%; (e) O_2, $Co(acac)_2$ (0.2 equiv), Et_3SiH (2.2 equiv), *t*-BuOOH (0.05 equiv), $(CH_2Cl)_2$; (f) $C_4F_9SO_2F$ (NfF), 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU), MeCN, −30 °C; SiO_2, 58% (2 steps); (g) BnOH, 4Å MS, SiO_2, 80 °C; (h) KH, **A**, THF, −78 to −40 °C, 68% (2 steps).

It was necessary to install the C15-ketone into olefin **11** without the intermediacy of the C15-free-alcohol because of the strong tendency of the alcohol to cyclize into the unreactive hemiacetal (Scheme 2). After many unsuccessful approaches, we developed a new two-step oxidation protocol from **11** to **17**. First, **11** was subjected to Et_3SiH and a catalytic amount of $Co(acac)_2$ and *t*-BuOOH under an oxygen atmosphere[8] to generate Et_3Si-peroxide **15**. Then, the Et_3Si group of **15** was directly exchanged to the nonafluoro-1-butanesulfonyl (Nf) group of **16** by the action of NfF[9] and DBU.[10] DBU induced the elimination of NfOH, providing the requisite C15-ketone **17** in one pot. During the silica gel purification, **17** was converted to bis-hemiacetal **14** through hydration.

To prepare for the α-alkoxy bridgehead radical reaction, the two hydroxy groups of **14** were differentially capped. In situ formation of triketone **17** from **14**, and subsequent attack of benzyl alcohol on the least hindered C15-ketone, were induced by acidic silica gel and 4 Å molecular sieves at 80 °C to generate hemiacetal **18**. Then, the remaining sterically congested C11-OH of **18** was converted to its potassium alkoxide, which reacted with the potently electrophilic pyridinium salt **A**, furnishing thiocarbonate **7**.[11] Non-ejection of benzyl alkoxide from the tertiary alkoxide of **18** again reflected the unusual stability of the six-membered hemiacetal structure.

Construction of the ABCDE-ring system **6** was accomplished from **7** in seven steps (Scheme 3). The first reaction demonstrated the efficiency of the bridgehead radical strategy for stereospecific C−C bond formation within this sterically demanding environment.[6b,12,13] Specifically, under these radical conditions, homolytic cleavage of the C11−O bond of thiocarbonate **7** proceeded to give α-alkoxy bridgehead radical **19**, which reacted with allyltributyltin[14] to set the C11-tetrasubstituted stereocenter of the ABDE-ring **20**. Next, the C6-hydroxy group was selectively liberated[15] from bis-MOM-ether **20** using $BF_3{\cdot}OEt_2$ and Me_2S[16] to generate alcohol **21**, which was oxidized with Dess−Martin reagent to afford C6-ketone **22**. Prior to further C6-functionalization, the terminal olefin of **22** was isomerized to the internal (*E*)-olefin of **23** using $PdCl_2(MeCN)_2$.[17] The MOM group of **23** was detached by applying the same reagent system to **21** at higher temperature, leading to **24**. Then, addition of (3-methylbut-3-en-1-yl)lithium[18] occurred regio- and stereoselectively at the C6-ketone of diketone **24** to produce **25**, presumably because the top face of the C6-ketone and both faces of the C3-ketone were sterically shielded by the highlighted functional groups in Figure 1. The C9-olefin of the elongated chain in turn underwent the ring-closing metathesis reaction with the isomerized C10-olefin upon use of second-generation Hoveyda−Grubbs catalyst (**B**),[19,20] resulting in formation of the six-membered C-ring **6**.

The two stereocenters at C9 and C10 were simultaneously introduced by hydroboration of the thus-constructed C9−C10 double bond (Scheme 3). Before hydroboration, protection of the C6-OH of **6** with its TMS ether was required to ensure the desired stereoselectivity.[21] Thus, diol **6** was first converted to bis-TMS-ether **26** using TMSOTf and pyridine. As the bulky TMS group of **26** blocked the top face (Figure 1), $BH_3{\cdot}THF$ approached from the concave face of the CD-ring, producing **27** as the sole isomer after oxidative work-up. TMS-introduction to the concomitantly deprotected C2-OH and

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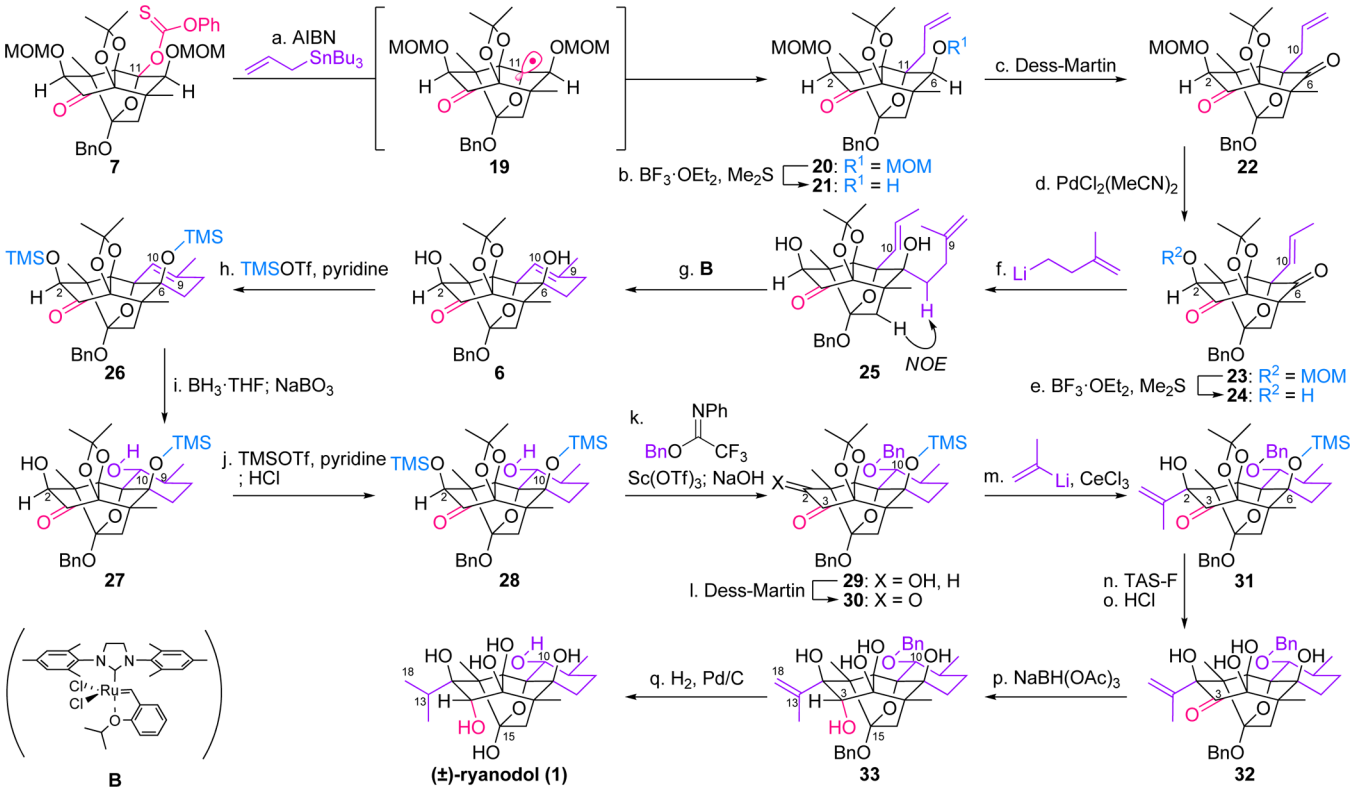
Scheme 3. Total Synthesis of Ryanodol[a]



[a]Reagents and conditions: (a) AIBN, $CH_2{=}CHCH_2SnBu_3$, benzene, reflux, 66%; (b) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2,−40 °C; (c) Dess−Martin reagent, $NaHCO_3$, CH_2Cl_2, 65% (2 steps); (d) $PdCl_2(MeCN)_2$ (0.2 equiv), $NaHCO_3$, toluene, 100 °C; (e) $BF_3{\cdot}OEt_2$, Me_2S, CH_2Cl_2,−20 °C, 86%, (2 steps); (f) $Me(C{=}CH_2)CH_2CH_2Br$, *t*-BuLi, THF, −78 °C, 84%; (g) **B**, toluene, 80 °C, 75%; (h) $Me_3SiOSO_2CF_3$ (TMSOTf), pyridine, $(CH_2Cl)_2$, 80 °C, 89%; (i) $BH_3{\cdot}THF$, THF; $NaBO_3{\cdot}4H_2O$; 1 M aq NaOH, 91%; (j) TMSOTf, pyridine, CH_2Cl_2, −78 °C; 10% HCl in MeOH, −40 °C, 87%; (k) $BnO(C{=}NPh)CF_3$, $Sc(OTf)_3$, 5Å MS, 1,4-dioxane; 1 M aq NaOH, 90%; (l) Dess−Martin reagent, CH_2Cl_2, 0 °C; (m) 2-bromopropene, *t*-BuLi, $CeCl_3$, THF, −78 °C, 21% (2 steps, recovered **30**, 53%); (n) tris(dimethylamino)sulfonium difluorotrimethylsilicate (TAS-F), DMF, 72%; (o) 1 M HCl in EtOAc, MeOH, 40 °C; (p) $NaBH(OAc)_3$, MeCN, 70 °C; aq KHF_2, MeOH, 35 °C; (q) H_2, Pd/C, MeOH, 87% (3 steps).

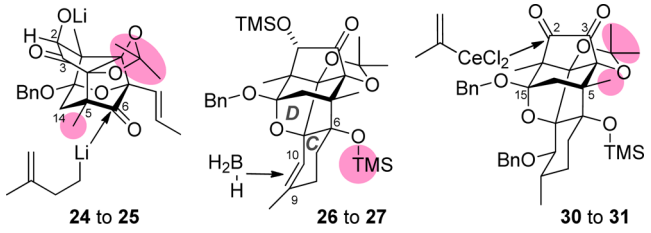


Figure 1. Rationale for three regio- and stereoselective reactions. Sterically cumbersome groups are highlighted in pink.

the newly generated C10-OH of **27** was followed by acid-promoted regioselective liberation of C10-OH to afford **28**. Treatment of **28** with $BnO(C{=}NPh)CF_3$[22] in the presence of $Sc(OTf)_3$ and subsequently with aqueous NaOH realized the preparation of **29** with C10-benzyloxy and C2-hydroxy groups. Dess−Martin oxidation of C2-alcohol **29** gave rise to C2-ketone **30**.

The total synthesis of ryanodol was accomplished from appropriately protected **30** in five steps, including the construction of C2, C3-consecutive stereocenters. A reagent combination of isopropenyllithium and $CeCl_3$[23] enabled nucleophilic addition of an isopropenyl unit to the C2-ketone of **30** from the opposite face of the acetonide. This reaction installed the correct C2-tetrasubstituted carbon of **31** without touching the C3-ketone that was kinetically protected by the acetonide and C5-methyl groups (Figure 1). TAS-F[24] then removed the TMS group at C6−OH of **31**, and the acetonide, which functioned as a robust protective group up to this stage, was cleaved using aqueous HCl to produce **32**.[25] Although the C3-ketone of the acetonide-protected intermediates was inert throughout the sequence **8** → **31**, $NaBH(OAc)_3$ reduction[26] of the C3-ketone of the deprotected tetraol **32** proceeded from the top face via a hydroxy-directed mechanism to produce pentaol **33** with the desired C3-stereochemistry. Lastly, hydrogenation of the C13-olefin and hydrogenolysis of the C10- and C15-Bn-ethers transformed **33** into fully synthetic (±)-ryanodol (**1**). Synthetic **1** was determined by ^1H NMR, ^{13}C NMR, and MS to be identical in all respects to an authentic sample of (+)-**1** obtained from the hydrolysis of (+)-ryanodine (**2**, Scheme 1).

In summary, ryanodol (**1**) was synthesized from the C_2-symmetric tricycle **8** in 22 steps by judiciously controlling the intrinsic reactivities of the three-dimensional structures of the polycyclic intermediates. Salient methodologies employed in our synthesis include (i) desymmetrizing C15-oxidation (**11** → **14**); (ii) differential functionalizations of bis-hemiacetal (**14** → **7**); (iii) *α*-alkoxy bridgehead radical reaction for stereospecific introduction of the C11-tetrasubstituted carbon (**7** → **20**); (iv) installation of the C6-carbon chain (**24** → **25**) and subsequent ring-closing metathesis reaction (**25** → **6**); (v) regio- and stereoselective hydroboration/oxidation (**26** → **27**); (vi)

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attachment of the C2-carbon chain using a cerium reagent (**30** → **31**); and (vi) hydroxy-directed reduction of the C3-ketone (**32** → **33**). In addition, facile synthesis of the ketone from the olefin using Co-catalyzed hydroperoxidation and NfF-promoted elimination should have wider application for the preparation of various hindered ketones beyond this target. The novel synthetic route developed here will accelerate the synthesis and biological studies of ryanodine and its artificial analogues for investigating the channel-mediated biological phenomena.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for all new compounds; experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Rogers, E. F.; Koniuszy, F. R.; Shavel, J., Jr.; Folkers, K. *J. Am. Chem. Soc.* **1948**, *70*, 3086. (b) Kelly, R. B.; Whittingham, D. J.; Wiesner, K. *Can. J. Chem.* **1951**, *29*, 905. (c) Kelly, R. B.; Whittingham, D. J.; Wiesner, K. *Chem. Ind.* **1952**, 857. (d) Wiesner, K.; Valenta, Z.; Findlay, J. A. *Tetrahedron Lett.* **1967**, *8*, 221. (e) Wiesner, K. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2656. (f) Wiesner, K. *Adv. Org. Chem.* **1972**, *8*, 295. (g) Srivastava, S. N.; Przybylska, M. *Can. J. Chem.* **1968**, *46*, 795.

(2) For recent reviews on ryanodine receptors, see: (a) *Ryanodine Receptors: Structure, Function and Dysfunction in Clinical Disease*; Wehrens, X. H. T., Marks, A. R., Eds.; Springer: New York, 2005. (b) Betzenhauser, M. J.; Marks, A. R. *Pflugers Arch.* **2010**, *460*, 467. (c) Mackrill, J. J. *Biochem. Pharmacol.* **2010**, *79*, 1535. (d) Van Petegem, F. *J. Biol. Chem.* **2012**, *287*, 31624.

(3) (a) Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Saint-Laurent, L.; Saintonge, R.; Soucy, P.; Ruest, L.; Deslongchamps, P. *Can. J. Chem.* **1979**, *57*, 3348. (b) Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H.-J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C.-C.; MacLachlan, F. N.; Maffrand, J.-P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. *Can. J. Chem.* **1990**, *68*, 186.

(4) For synthetic studies of ryanodol, see: (a) Sieburth, S. M.; Santos, E. D. *Tetrahedron Lett.* **1994**, *35*, 8127. (b) Wood, J. L.; Graeber, J. K.; Njardarson, J. T. *Tetrahedron* **2003**, *59*, 8855.

(5) For a review on the structure−activity relationship studies of ryanodine, see: Sutko, J. L.; Airey, J. A.; Welch, W.; Ruest, L. *Pharmacol. Rev.* **1997**, *49*, 53.

(6) (a) Hagiwara, K.; Himuro, M.; Hirama, M.; Inoue, M. *Tetrahedron Lett.* **2009**, *50*, 1035. (b) Urabe, D.; Nagatomo, M.; Hagiwara, K.; Masuda, K.; Inoue, M. *Chem. Sci.* **2013**, *4*, 1615. For synthesis of enantiopure intermediates, see: (c) Iwatsu, M.; Urabe, D.; Inoue, M. *Heterocycles* **2010**, *82*, 491. (d) Tabuchi, T.; Urabe, D.; Inoue, M. *Beilstein J. Org. Chem.* **2013**, *9*, 655.

(7) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. For reviews, see: (b) Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.* **1981**, *53*, 15. (c) Crich, D.; Quintero, L. *Chem. Rev.* **1989**, *89*, 1413.

(8) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 573. (b) Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1305. (c) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. *Org. Lett.* **2002**, *4*, 3595.

(9) For a review on NfF, see: Vorbrüggen, H. *Synthesis* **2008**, 1165.

(10) Gembus, V.; Marsais, F.; Levacher, V. *Synlett* **2008**, 1463.

(11) (a) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932. (b) Pettus, T. R. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160.

(12) For application of α-bridgehead radical strategy for assembly of complex structures, see: (a) Urabe, D.; Yamaguchi, H.; Inoue, M. *Org. Lett.* **2011**, *13*, 4778. (b) Kamimura, D.; Urabe, D.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013**, *15*, 5122. (c) Murai, K.; Katoh, S.; Urabe, D.; Inoue, M. *Chem. Sci.* **2013**, *4*, 2364.

(13) For a review on bridgehead radicals, see: (a) Walton, J. C. *Chem. Soc. Rev.* **1992**, *21*, 105. For representative examples of application of bridgehead radicals in the context of natural product synthesis, see: (b) Kraus, G. A.; Andersh, B.; Su, Q.; Shi, J. *Tetrahedron Lett.* **1993**, *34*, 1741. (c) Kraus, G. A.; Su, Q. *Synlett* **1994**, 237. (d) Kim, S.; Cheong, J. H. *Synlett* **1997**, 947. (e) Tsukano, C.; Siegel, D. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8840.

(14) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829.

(15) C6-OMOM of **20** was selectively deprotected, presumably because the electron-withdrawing nature of the C3-ketone would decrease the Lewis basicity of C2-OMOM group toward $BF_3{\cdot}OEt_2$ in comparison to that of the C6-OMOM group.

(16) (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662. (b) Sasaki, M.; Inoue, M.; Takamatsu, K.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 9399.

(17) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.

(18) Leach, A. G.; Wang, R.; Wohlhieter, G. E.; Khan, S. I.; Jung, M. E.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 4271.

(19) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(20) For recent reviews on ring-closing metathesis reactions, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (b) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

(21) When hydroboration/oxidation was performed without the TMS group at C6-OH, the undesired isomer was obtained as the major product.

(22) Okada, Y.; Ohtsu, M.; Bando, M.; Yamada, H. *Chem. Lett.* **2007**, 992.

(23) (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) Takeda, N.; Imamoto, T. *Org. Synth.* **1999**, *76*, 228.

(24) (a) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. *J. Am. Chem. Soc.* **1980**, *102*, 1223. (b) Scheidt, K. A.; Chen, H.; Follows, B. C.; Chemler, S. R.; Coffey, D. S.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 6436.

(25) Soda-lime and quartz glassware were used for the reactions and purification of polyols **32**, **33**, and **1** because these form the stable borate with B_2O_3 leached from borosilicate glassware.

(26) (a) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535. (b) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (c) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287. (d) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.