Natural Product Synthesis

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# Asymmetric Total Synthesis of Solandelactone E: Stereocontrolled Synthesis of the 2-ene-1,4-diol Core through a Lithiation–Borylation–Allylation Sequence**

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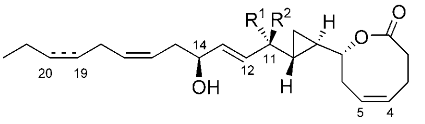
The solandelactones comprise a novel class of oxygenated fatty acids that contain an eight-membered lactone linked to a *trans* cyclopropane, and were first isolated by Shin and coworkers in 1996[1] from the hydroid *Solanderia secunda*. These compounds belong to a wider group of marine oxylipins that contain the linked lactone and cyclopropane unit, including halicholactone[2] and the constanolactones.[3] Initial assignment of structure and absolute stereochemistry was based primarily on NMR studies, which led to two sets of compounds depending on their configuration at C11: *R* configuration for A, C, E, and G; *S* configuration for B, D, F, and H. However, the experimental data for synthetic solandelactone "F", which had been synthesized by Martin and coworkers,[4] matched the data for solandelactone E, thus indicating that the two sets of compounds had been incorrectly assigned. Further syntheses by White et al.[5] as well as Pietruszka and Rieche[6] confirmed that the configuration at C11 in all of the solandelactones A–H should be depicted as in Scheme 1.

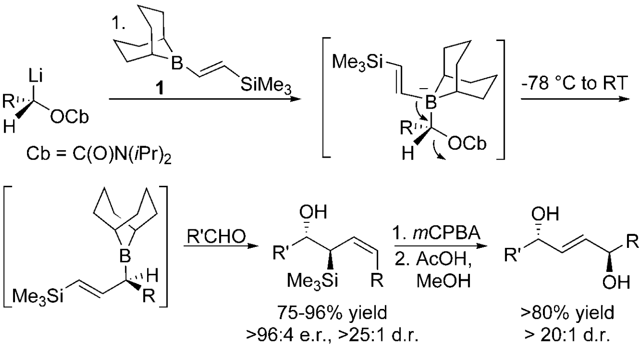


| $R^1$ = H, $R^2$ = OH: | $R^1$ = OH, $R^2$ = H: |
|---|---|
| solandelactone B | solandelactone A |
| solandelactone D ($\Delta^{19,20}$) | solandelactone C ($\Delta^{19,20}$) |
| solandelactone F ($\Delta^{4,5}$) | solandelactone E ($\Delta^{4,5}$) |
| solandelactone H ($\Delta^{4,5}$, $\Delta^{19,20}$) | solandelactone G ($\Delta^{4,5}$, $\Delta^{19,20}$) |

***Scheme 1.*** Revised structure of solandelactones A–H.

Almost all syntheses of the solandelactones, constanolactones,[7,8] and halicholactone[9–11] introduce the aliphatic side chain (e.g. C12–C22 in solandelactone) through a Nozaki–Hiyama–Kishi reaction between a vinyl organometallic reagent and the cyclopropyl aldehyde. Unfortunately, this reaction occurs with very poor stereocontrol. In fact, it has been shown that the configuration at C11 ($\approx 2{:}1$) is controlled predominantly by the configuration at C14 and not by the configuration of the cyclopropane ring.[6,9] Martin's synthesis provides a unique strategy to access this class of compounds, which features high levels of stereocontrol.[4] His strategy avoids the C11–C12 disconnection but this inevitably makes the synthesis more linear.

Our research group has recently described a new method for the stereocontrolled synthesis of *anti*-1,4-diols[12] which seemed to offer an ideal solution to achieving high levels of stereocontrol at C11 while maintaining a convergent synthesis. This method comprised of the coupling of a lithiated carbamate, β-silyl vinyl borane **1**, and an aldehyde, which gave an allyl silane in high yield with high enantio- and diastereoselectivity. Subsequent epoxidation and acid-catalyzed elimination gave 2-ene-1,4-diols[13] with high enantio- and diastereoselectivity (Scheme 2). It was essential to use an unhindered diamine or diamine-free conditions in the reaction of the lithiated carbamate with the borane to achieve high enantioselectivity.[12a] Herein we describe the total synthesis of solandelactone E in a concise manner with high levels of control over the configuration of all stereogenic centers, thus establishing our methodology as a robust reaction for the synthesis of complex molecules.



***Scheme 2.*** New method for synthesis of allyl silanes and 2-ene-1,4-diols. *m*CPBA = *meta*-chloroperoxybenzoic acid.

Our aim was to utilize our three-component coupling reaction to install the C12–C22 aliphatic chain. Thus, disconnection across the C11–12 and C13–14 bonds would lead to aldehyde **2**, β-silyl vinyl borane **1,** and carbamate **3** (Scheme 3). It was envisaged that aldehyde **2** could be obtained through **4**, which itself could be accessed from **5** through epoxidation and Taber cyclopropanation.[14]

Synthesis of aldehyde **2** was initiated with indium-mediated coupling of allyl bromide and propargylic alcohol **6** (Scheme 4).[15] Subsequent Sharpless epoxidation[16] gave

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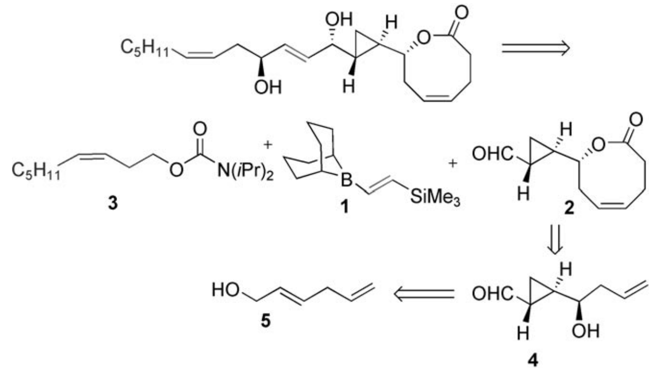
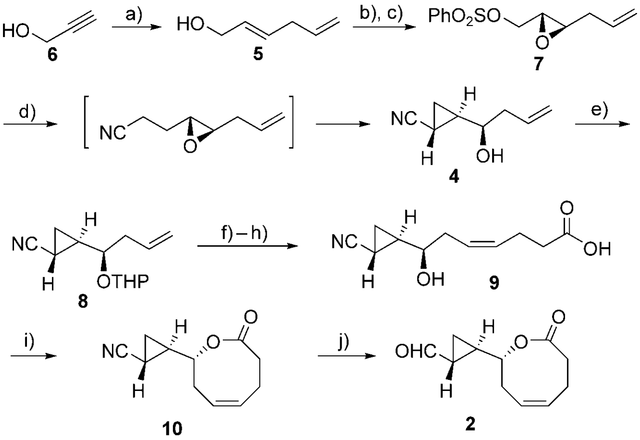


*Scheme 3.* Retrosynthetic route to solandelactone E.



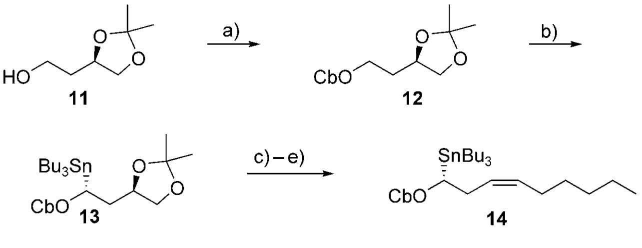
*Scheme 4.* Synthesis of aldehyde **2**. Reagents and conditions: a) allyl bromide, In, THF, RT, 77%; b) (−)-DET, $Ti(OiPr)_4$, tBuOOH, $CH_2Cl_2$, −20 °C, 75%, e.r. 97:3; c) $PhSO_2Cl$, $Et_3N$, DMAP, $CH_2Cl_2$, RT, 90%; d) NaHMDS, $CH_3CN$, THF, −78 °C–0 °C, 91% d.r. 5.6:1 (separable); e) DHP, PPTS, $CH_2Cl_2$, RT, 94%; f) $K_2OsO_4\cdot 2H_2O$, $NaIO_4$, 2,6-lutidine, $H_2O$/dioxane (1:3, RT; g) $HO_2C(CH_2)_3PPh_3Br$, NaHMDS, THF, −78 °C–RT, $Z/E > 9:1$; h) HCl (aq), RT, 59% over three steps; i) 1. 1,3,5-trichlorobenzoyl chloride, $Et_3N$, THF, RT; 2. DMAP, toluene, 90 °C–60 °C, 79%; j) Raney–Ni, $NaH_2PO_2\cdot H_2O$, pyridine/$H_2O$/AcOH (2:1:1), RT, 87%. DET = diethyl tartrate, DHP = 3,4-dihydro-2*H*-pyran, DMAP = 4-dimethylaminopyridine, HMDS = bis(trimethylsilyl)amide, PPTS = pyridinium *p*-toluenesulfonate, THF = tetrahydrofuran, THP = tetrahydropyranyl.

epoxide **6** in excellent enantiomeric ratio (e.r.). Notably, the configuration of the epoxide is utilized to establish the three stereogenic centers in aldehyde **2**. Thus, after activation with a benzenesulfonyl group, treatment of epoxide **7** with NaHMDS and two equivalents of acetonitrile, through a modification of Taber's method,[14] gave cyclopropane **4** as a separable mixture of diastereomers (5.6:1) in 91% yield. Following protection of the alcohol as its THP ether **8**, the alkene was subjected to oxidative cleavage, Wittig olefination, and removal of the THP group. Yamaguchi lactonization of acid **9** then gave the eight-membered lactone **10**.[6] This sequence was considerably more rewarding than esterification of **4** with 5-pentenoic acid and subsequent ring-closing metathesis.[17] Finally, we needed to convert the nitrile into an aldehyde in the presence of an olefin and a lactone—a procedure that initially presented some challenges. Attempts using diisobutylaluminum hydride led to a mixture of products but Raney–nickel with sodium hypophosphite[18] gave **2** as a single product in high yield. Although aldehyde **2** had previously been synthesized, our route represents a significant decrease in the number of steps (10 steps vs. 13 steps[5,19] or 14 steps[6]), with high stereocontrol and only a single protecting-group manipulation.

In accordance with our synthetic method, our initial plan was to treat carbamate **3** (synthesized by carbamoylation of the commercially available alcohol) directly with *s*BuLi in the presence of O'Brien's (+)-sparteine surrogate[20] to give the desired enantioenriched lithiated carbamate. However, treatment of **3** with *s*BuLi and TMEDA resulted predominantly in elimination of the carbamate (allylic deprotonation) rather than deprotonation adjacent to the carbamate moiety. Although carbamates bearing unsaturation at more remote positions have been successfully employed, there is clearly a limitation in the use of homoallylic carbamates. This discovery could have represented a significant stumbling block for the scope of our method. However, we were able to eliminate the problem by making use of a stannane as a latent lithiated species.[21] Thus, tin–lithium exchange of **14** was expected to furnish the same lithiated carbamate required for the key three-component coupling reaction.

Stannane **14** was prepared as shown in Scheme 5. After the conversion of the commercially available alcohol **11** into carbamate **12**, substrate-directed lithiation and trapping with $Bu_3SnCl$, as described by Hoppe and co-workers,[22] furnished **13** as an inseparable mixture with d.r. 10:1. Installation of the required aliphatic chain was achieved by a sequence of removal of the acetal protecting group, oxidative cleavage, and Wittig olefination to give stannane **14**.

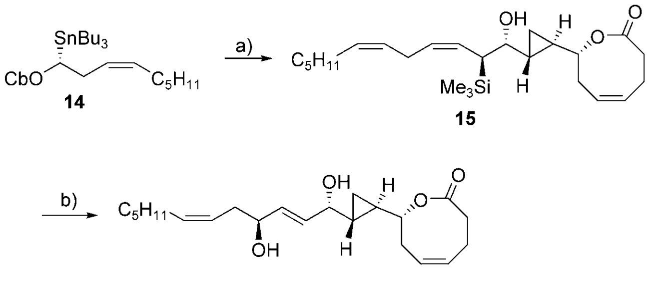
With the three components for our coupling reaction in hand, we subjected them to our standard lithiation–borylation–allylboration procedure.[12] However, **15** was only obtained in 15% yield. The major impurity was formed by attack of the lithiated carbamate on aldehyde **2**, thus indicating that the reaction with the borane was incomplete. Visual examination of the reaction mixture following lithiation showed it to be highly viscous at low temperature and so we suspected that the problem lay in incomplete mixing with the borane, thus resulting in competing addition to the aldehyde. We were able to solve this problem by adding TMEDA after *n*BuLi. This led to a much more mobile reaction mixture at low temperature and after the addition of borane **1** and aldehyde **2**, gave **15** as a separable mixture with



*Scheme 5.* Route to chiral stannane carbamate **14**. Reagents and conditions: a) *N*,*N*-diisopropyl carbamoyl chloride, NaH, THF, reflux, 85%; b) *s*BuLi, $Et_2O$; then $Bu_3SnCl$, −78 °C, 42% (84% brsm), d.r. 10:1 (inseparable); c) 1 M HCl (aq), MeOH, RT; d) $NaHCO_3$, $NaIO_4$, RT; e) $C_6H_{13}PPh_3Br$, NaHMDS, THF, −78 °C–RT, 80% over three steps. brsm = based on recovered starting material.

d.r. 10:1 in 73 % yield. As the lithiated carbamate had an e.r. of 10:1, the diastereoselectivity observed shows that the sequence of lithiation–borylation–allylation sequence occurred with complete retention of configuration in the borylation step (as a consequence of using an unhindered diamine complexed to the lithiated carbamate[12a]) and complete control of the configuration in the allylboration step.[23]

The penultimate step of the synthesis required selective epoxidation of the allyl silane without oxidation of the two other olefin groups present. This was achieved by utilizing the directing effect of the homoallylic alcohol with Ti(O*i*Pr)$_4$/*t*BuOOH[24] which, after acid-catalyzed rearrangement, gave solandelactone E as a single diastereoisomer in 68 % yield over two steps (Scheme 6). The spectroscopic data matched exactly with those of natural and synthetic solandelactone E.[1,4–6]



*Scheme 6.* Completion of solandelactone E. Reagents and conditions: a) *n*BuLi, TMEDA, Et$_2$O; then borane **1**; then aldehyde **2**, 73 %, d.r. 10:1 (separable); b) *t*BuOOH, Ti(O*i*Pr)$_4$, M.S. (4 Å), CH$_2$Cl$_2$; AcOH, MeOH, 68 % over two steps. M.S. = molecular sieves, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

In conclusion, we have completed a short (13 steps, longest linear sequence) and highly selective synthesis of solandelactone E. The key steps included Sharpless epoxidation, Taber cyclopropanation, chemoselective reduction of a nitrile to an aldehyde, and our own lithiation–borylation–allylation sequence on a highly functionalized substrate. Not only does the completed synthesis establish the method for application to complex targets, it also solves the problem of poor stereocontrol at C11 that had dogged many previous syntheses of this class of molecules.

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**Keywords:** allyl silanes · 1,4-ene-diols · lithiation–borylation · natural products · total synthesis

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