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# Total Synthesis of (+)-Erogorgiaene Using Lithiation−Borylation Methodology, and Stereoselective Synthesis of Each of Its Diastereoisomers

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Supporting Information

**ABSTRACT:** A short (8 steps) synthesis of (+)-erogorgiaene in 44% overall yield from *p*-methylacetophenone is described. Key steps include lithiation/borylation−protodeboronation to build up the molecule and control the stereochemistry at C1 and C4. The C11 stereochemistry was similarly set up by using lithiation/borylation methodology. The use of a mixed, unhindered borane in the lithiation/borylation reaction proved critical to success in the reaction of the tetralone-derived carbamate to control the C4 stereochemistry. The power of the reagent controlled methodology is illustrated in the stereocontrolled synthesis of all of the diastereomers of (+)-erogorgiaene.

(+)-Erogorgiaene (**1**, Figure 1) is a marine diterpene natural product isolated from the West Indian sea whip, *psueudopterogorgia elisabethae*, which shows promising activity against *Mycobacterium tuberculosis* $H_{37}Rv$.[1] It is one member of a family of related bioactive metabolites that have been isolated from the same marine organism (Figure 1).[2] Although erogorgiaene is not complex, the three stereogenic centers contained in the molecule coupled with the lack of functional groups proximal to branch points significantly amplify the synthetic challenge. Nevertheless, the total synthesis of erogorgiaene has been reported by Hoveyda,[3] Davies,[4] and Yadav[5] in 11 to 18 steps. In these approaches, functional groups are often added to enable key disconnections to be made, which inevitably leads to additional steps. For step economy, it would be preferable to disconnect the molecule directly at branch points, without the addition of functional groups elsewhere.

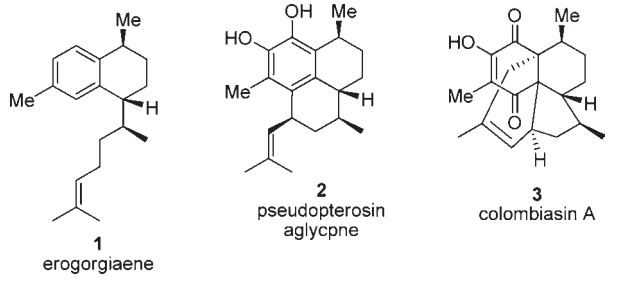



**Figure 1.** Erogorgiaene and other closely related natural products isolated from the West Indian sea whip.

We recently reported the lithiation/borylation−protodeboronation (LBP) of secondary carbamates for the stereocontrolled synthesis of aryldialkylmethines.[6] The lithiation/borylation methodology involves the reaction of lithiated carbamates with boronic esters, which occurs with retention of configuration, and with boranes, which react with inversion (Figure 2).[7] Precoordination of the oxygen of the boronic ester with lithium is believed to be responsible for the delivery of boron with retention. This leads to tertiary boranes and boronic esters with high enantioselectivity. In this paper, we describe the application of this methodology to a short stereocontrolled synthesis of (+)-erogorgiaene. Furthermore, by targeting all possible diastereoisomers of the natural product, we demonstrate the broad synthetic utility of the lithiation−borylation methodology and the power of reagent control.

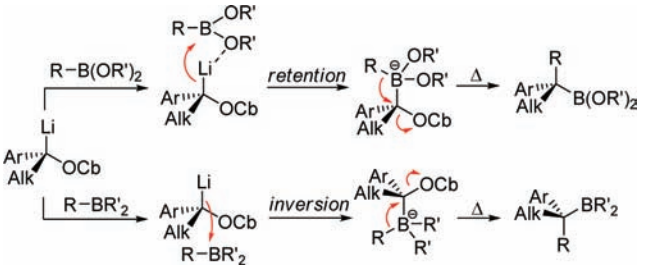



**Figure 2.** Lithiation/borylation with boronic esters and boranes leading to opposite enantiomers.

In our retrosynthetic analysis, and using the lithiation/borylation−protodeboronation reaction as a key step, disconnection of the $C^4-C^{11}$ bond led us back to the *trans* carbamate **4** and borane **5** or the *cis* carbamate **6** and the boronic ester **7** (Figure 3). We were aware that this step would be challenging, since tetralone-derived carbamates always gave the lowest diastereoselectivity of all of the carbamates we have explored,[8] and we therefore wanted to keep both options open. The required boron reagent could be obtained directly using our lithiation/borylation reaction of primary carbamates.[9] Carbamates **4** and **6** can both be derived from ketone **8** using Noyori reduction,[10] which itself could be obtained from ester **9**. Ester **9** could be accessed through another LBP of carbamate **10** with the commercially available boronic ester **11**.

**Received:** August 19, 2011
**Published:** September 21, 2011





dx.doi.org/10.1021/ja207869f | *J. Am. Chem. Soc.* 2011, 133, 16798–16801

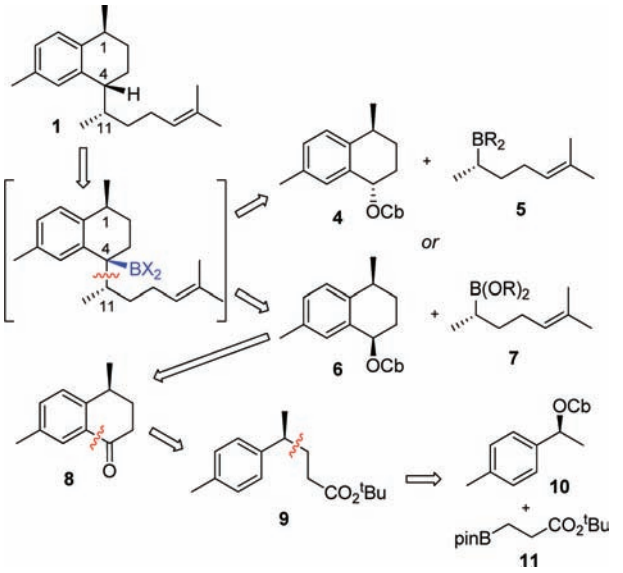
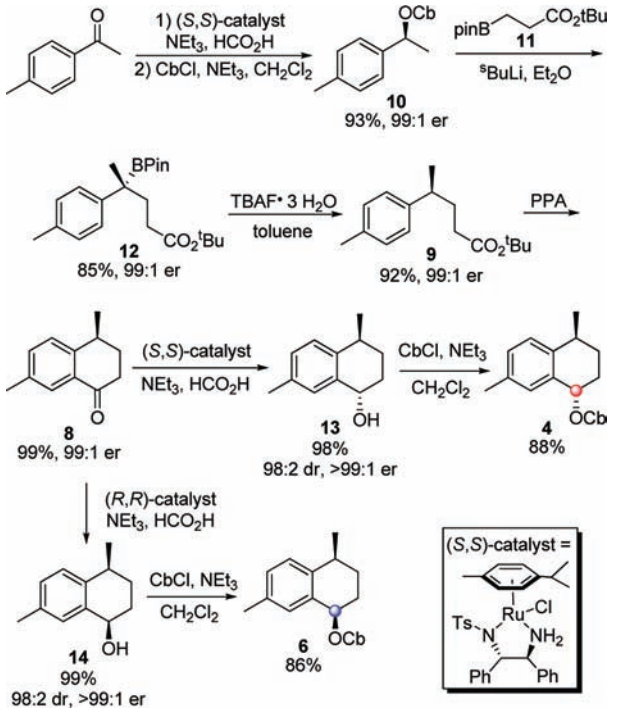



**Figure 3.** Retrosynthetic analysis of (+)-erogorgiaene.

**Scheme 1. Synthesis of Key Carbamates 4 and 6**




Our synthesis began by Noyori reduction of *p*-methylacetophenone, which gave the alcohol in 99% yield and 99:1 er, followed by carbamoylation with *N,N*-diisopropylcarbamoyl chloride (CbCl) to furnish carbamate **10** (Scheme 1). Treatment with *s*-BuLi, followed by addition of boronic ester **11**, furnished tertiary boronic ester **12**, which was subsequently treated with TBAF to give ester **9** with complete retention of stereochemistry in high yield. Treatment with polyphosphoric acid (PPA) gave ketone **8**, which was reduced with either the (*S,S*)- or (*R,R*)-Noyori catalyst to give the corresponding *trans* and *cis* alcohols **13** and **14** in high yield and essentially complete

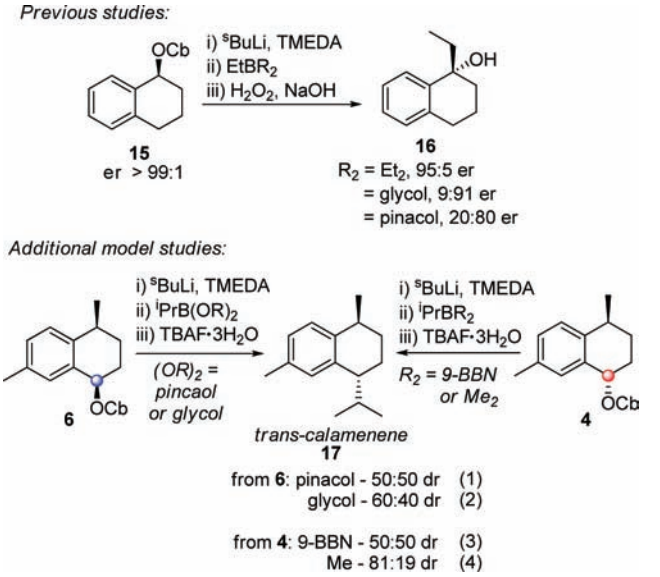


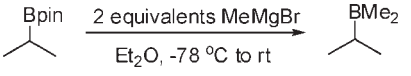

**Figure 4.** Model studies of tetralone-based carbamates and their selectivity in lithiation/borylation reactions.

diastereoselectivity (>99:1 er, 98:2 dr in both cases). Finally, carbamoylation of these two alcohols provided the desired carbamate fragments **4** and **6**.

Before we embarked on the final LBP reaction, we decided to investigate a model reaction with simpler isopropyl boron reagents. Previously, we had found that carbamate **15** reacted with high er with unhindered ethylboronic acid glycol ester (9:91) or $Et_3B$ (95:5), while ethylboronic acid pinacol ester gave a 20:80 ratio of enantiomers (Figure 4).[7] Unfortunately, reaction of carbamate **15** with isopropylboronic acid glycol ester gave a 50:50 ratio of enantiomers. These results highlighted the problems associated with tetralone-derived carbamates and their reactions with boronic esters bearing hindered substituents. This was further borne out in our additional model studies.

Unsurprisingly, reaction of carbamate **6** with isopropylboronic acid pinacol ester or the less hindered isopropylboronic acid glycol ester gave an ~1:1 ratio of diastereomers (Figure 4, eqs 1, 2).[11] We therefore turned to boranes where higher selectivity had been observed (e.g., **15** with $Et_3B$). However, reaction of carbamate **4** with B-$^i$Pr-9-BBN gave similarly poor dr (Figure 4, eq 3). We clearly required a much less hindered borane and considered the use of $^i$PrBMe$_2$, but the issue of which of the three groups would migrate was a concern. Although sterically hindered groups (e.g., thexyl) have been used as nonmigrating groups in reactions of boranes, occasionally very small groups (e.g., Me) have too.[12,13] Furthermore, we had found that in reactions of primary lithiated carbamates with boronic esters, MeBpin reacted considerably more slowly than EtBpin.[13b]

Mixed borane $^i$PrBMe$_2$ was therefore prepared as shown in eq 5, simply by the addition of 2 equiv of MeMgBr to the pinacol ester,[14] and employed in the lithiation/borylation reaction.



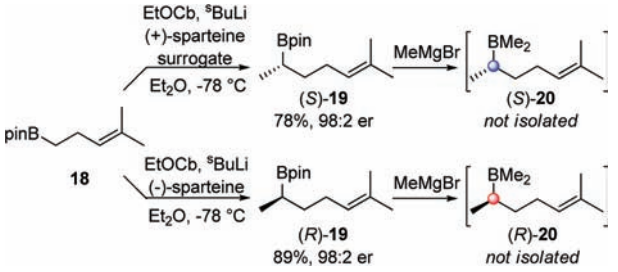

Following protodeboronation with TBAF,[15] product **17** was obtained with a 81:19 dr (Figure 4, eq 4). As expected, exclusive


dx.doi.org/10.1021/ja207869f |*J. Am. Chem. Soc.* 2011, 133, 16798–16801

migration of the isopropyl group over the methyl groups was observed. Purification led to a 81:19 mixture by $^1$H NMR of the *trans* and *cis* diastereomers of the natural product, calamenene (**17**), which were identical to that reported previously.[16] The synthesis of *trans*-calamenene as the major diastereomer confirmed that reaction of the lithiated carbamate with the borane occurred with inversion of stereochemistry[7] and that protodeboronation occurred with retention of stereochemistry.[15]

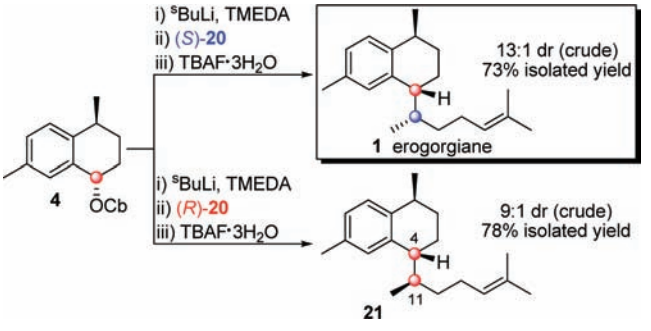
With this result, we continued in our pursuit of the natural product (+)-erogorgiaene. The required borane was prepared as shown in Scheme 2. Thus, lithiation of *N,N*-diisopropyl ethylcarbamate (EtOCb) in the presence of O'Brien's (+)- sparteine surrogate[17] followed by addition of homoallylboronic ester **18** gave boronic ester (*S*)-**19**. The boronic ester was converted into mixed dimethyl borane (*S*)-**20**, as before, by treatment with 2 equiv of MeMgBr.[14]

**Scheme 2. Synthesis of Mixed Boranes (*S*)- and (*R*)-20**



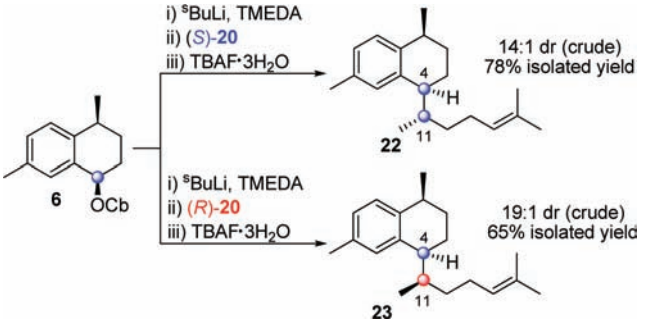

Borane (*S*)-**20** was not isolated but directly added to the lithiated carbamate derived from **4** (Scheme 3). Again without isolation, direct treatment of the reaction mixture with TBAF furnished crude **1** as a 13:1 mixture of diastereomers, as analyzed by GC/MS. Purification by flash chromatography led to pure (+)-erogorgiaene (**1**) in 73% yield. The synthetic material was identical in all respects to previously reported data for (+)-**1**. The asymmetric synthesis of the natural product was thus completed in just 8 steps from *p*-methylacetophenone and 44% overall yield, with high levels of stereocontrol over the three stereogenic centers.

**Scheme 3. Synthesis of (+)-Erogorgiaene (1) and C-11 Epimer 23**




The power and potential of this methodology is further illustrated in the stereoselective preparation of all possible diastereomers of **1**. Thus, borane (*R*)-**20** was prepared using (−)-sparteine in the lithiation−borylation reaction (Scheme 2). Treatment of the

**Scheme 4. Synthesis of C-4 Epimer 22 and C-4/C-11 Diepimer 23 of Erogorgiane**




lithiated carbamate derived from **4** with (*R*)-**20** as before gave C-11 epi-erogorgiaene **21** as a 9:1 ratio of diastereomers, which, after purification, provided pure **21** in 78% yield (Scheme 3). In a similar fashion, reaction of *cis* carbamate **6** with boranes (*S*)-**20** and (*R*)-**20** gave C-4 epi-erogorgiane[18] **22** and C-4/C-11 diepi-erogorgiane[18] **23** as a 14:1 and 19:1 mixture of diastereomers, respectively (Scheme 4). These results indicate that the stereochemical outcome of the key lithiation/borylation reaction of the tetralone-derived carbamate is not significantly affected by the pre-existing stereogenic centers in either the carbamate (at C1) or the borane (i.e., minimal matched and mismatched stereochemical effects), only by the nature and steric hindrance of the boron reagent.

In summary, we have described an 8 step synthesis of (+)-erogorgiaene in 44% overall yield using lithiation/borylation methodology to control all three stereogenic centers. The use of mixed, unhindered boranes in the lithiation/borylation reaction proved pivotal to success due to the sometimes low selectivity of the tetralone-derived carbamates toward boronic esters. Also noteworthy is the finding that TBAF, which had been previously used for stereoselective protodeboronation of tertiary boronic esters, is also suitable for tertiary boranes. In addition, the utility of the methodology is illustrated in the stereocontrolled synthesis of not only (+)-erogorgiaene but also each of the remaining diastereomers, all of which proceeded with equal ease and high yield and high selectivity. This illustrates the power of reagent controlled methodology, especially when it dominates so completely over substrate control. The brevity of the synthesis stems from exploiting strategic disconnections at branch points, which eliminate the need for additional functional group manipulations, redox processes, and protecting groups.

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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## ■ ACKNOWLEDGMENT

We thank EPSRC and the European Research Council (FP7/2007-2013, ERC Grant No. 246785) for financial support. V.K.A. thanks the Royal Society for a Wolfson Research Merit Award

and EPSRC for a Senior Research Fellowship. S.N. thanks the DFG for a research fellowship. We thank Inochem-Frontier Scientific for the generous donation of boronic acids and boronic esters.

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(8) Indanyl-derived lithiated carbamates react with boronic esters with very high selectivity (retention), but with lower selectivity with boranes (retention still). Acyclic secondary benzylic lithiated carbamates react with very high selectivity with both boronic esters (retention) and boranes (inversion). Also, see ref 7.

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(11) Both oxidation and protodeboronation of the boronic ester product arising from carbamate **4** or **6** and $^{i}$PrBR$_2$ provided the same result, indicating that the degradation in stereoselectivity was occurring during the lithiation/borylation step.

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(13) In the case of the small Me substituent, the short C−B bond length in the boron−ate complex makes it a stronger bond and so the barrier to migration is greater (TS is reactant-like). See: (a) Bottoni, A.; Lombardo, M.; Neri, A.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 3397–3405. (b) Larouche-Gauthier, R.; Fletcher, C. J.; Couto, I.; Aggarwal, V. K. *Chem. Commun.* 2011, DOI: 10.1039/c1cc14469c. Note that compression of the bond angles occurs in the migrating group at the transition state for migration. This effect should be especially important for a highly substituted migrating carbon and will disfavour the migration of hindered groups. Thus, both methyl and thexyl groups, which clearly are at the opposite extremes of steric demand, are both often nonmigrating groups. See ref 12 for a more complete discussion on the complexity of the issues involved.

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