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Application of the *B*-Alkyl Suzuki–Miyaura Cross-Coupling Reaction to the Stereoselective Synthesis of Analogues of (3*S*)-Oxidosqualene

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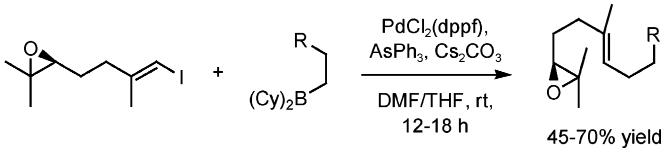
ABSTRACT



A general method is described for the direct and stereoselective synthesis of epoxypolyenes via Suzuki–Miyaura cross-coupling reaction of 1-iodoalkenes with *B*-alkylboron compounds. It allows for the straightforward and convergent assembly of compounds that are structurally similar to (3*S*)-oxidosqualene, an important intermediate in steroid biosynthesis.

The reported study is part of a project that investigates the cyclization behavior of several analogues of (3*S*)-oxidosqualene,[1] the natural substrate for the intriguing enzymatic polycyclization reaction in the steroid biosynthesis.[2,3]

Initial attempts to assemble analogues such as **1** or **2** (Figure 1) from advanced intermediates **3**, **5**, **8**, and **11** (see Schemes 1 and 2) using recently established coupling reactions in this field[4,5] were frustrated by the failure to prepare any suitable organometallic reagents from both iodoalkenes **3** and **5** or from derivatives of **11**.

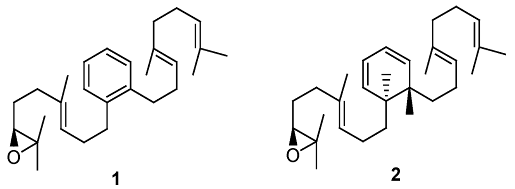
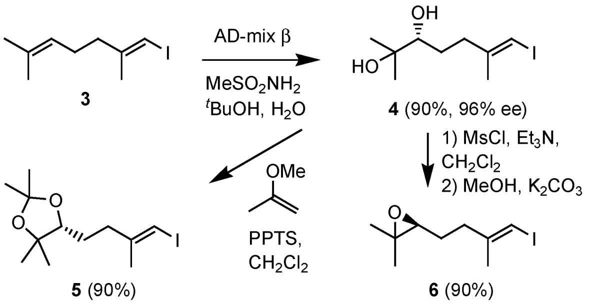

1 **2**

Figure 1. Analogues of (3*S*)-oxidosqualene.

We were, however, able to achieve the sp^2−sp^3 C−C bond applying the *B*-alkyl Suzuki−Miyaura cross-coupling reaction.[6,7]

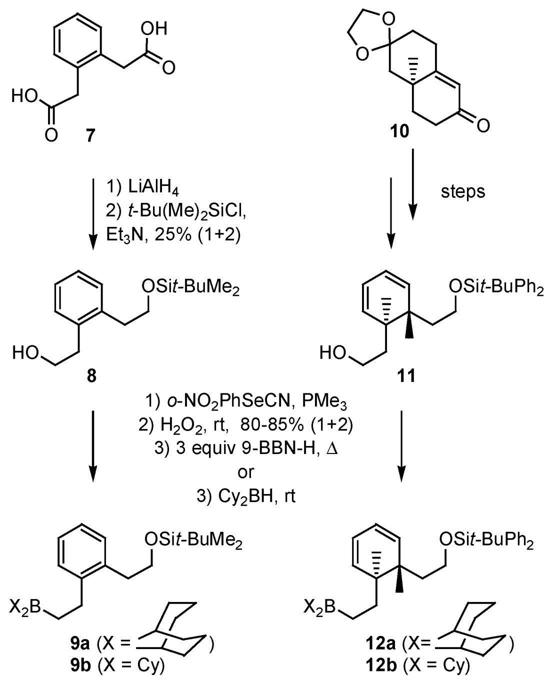
The electrophiles **5** and **6**, respectively, bearing a protected (*R*)-diol and the required (*S*)-epoxide (of which the acetonide is a latent form), were efficiently obtained starting from the known iodoalkene **3**[8] via a highly regio- and enantioselective

Scheme 1



10.1021/ol061962z CCC: $33.50

Scheme 2

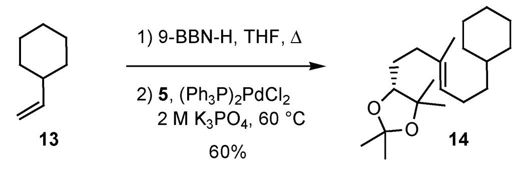


Sharpless asymmetric dihydroxylation reaction (Scheme 1).[9,10]

The central part of target structure **1** was easily derived from the readily available diacid **7** (Scheme 2). For target polyene **2**, the advanced key intermediate **11** was synthesized from the known (S)-methyloctalone **10** (Scheme 2).[11,12] The corresponding B-alkylboron species **9a**,**b** and **12a**,**b** could be conveniently prepared in situ via hydroboration of the alkenes derived from intermediates **8** and **11**, using the Grieco−Sharpless elimination protocol.[13] Hydroboration reactions with 9-borabicyclo[3.3.1]nonane were found to be very sluggish even under the harsh conditions used, especially in the case of the neopentyl vinyl substrates derived from **11**. In contrast, reactions with dicyclohexylborane proceeded very smoothly under mild conditions.

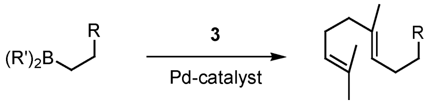
A first successful coupling of iodoalkene **5** with model alkene substrate **13** showed the feasibility of the approach via Suzuki reaction (Scheme 3).

Scheme 3



We then proceeded to investigate the cross-coupling of B-alkylboron substrates **9a**,**b** and **12a**,**b**. The results of the coupling experiments with iododiene **3** and these alkylborane species are outlined in Table 1.

Table 1. Cross-Coupling Reactions of Some B-Alkylboron Compounds with **3** under Various Conditions



entry	substrate	product	procedure[a]	temp (°C)	time (h)	yield[b] (%)
1	**9a**	**15**	A	60	3	64
2	**12b**	**17**	A	60	3	trace
3	**12b**	**17**	B	60	3	10[c]
4	**12b**	**17**	B	rt	18	45
5	**12b**	**17**	B[d]	rt	20 + 20	80
6	**9b**	**15**	B[d]	rt	20 + 20	75

[a] Reactions were conducted by adding 1.0 equiv of freshly prepared B-alkylboron reagent in THF/H$_2$O to (i) a stirred solution of 0.96 equiv of **3**, 0.10 equiv of PdCl$_2$(PPh$_3$)$_2$, and 2.0 equiv of 3 M K$_3$PO$_4$ in DMF (procedure A) or (ii) a stirred suspension of 0.96 equiv of **3**, 0.10 equiv of PdCl$_2$(dppf), 0.10 equiv of Ph$_3$As, and 2.0 equiv of Cs$_2$CO$_3$ in DMF (procedure B). [b] Isolated yields after column chromatography. [c] Isolated with minor amounts of inseparable impurities from the complex reaction mixture. [d] Another 0.25 equiv of **3** was added during the course of the reaction.

Application of the classical high-temperature conditions (procedure A) used in the model experiment (Scheme 3) gave satisfactory results for **9a** but were unsuccessful for the more demanding substrate **12b** (entries 1 and 2, Table 1). From a small screening of the most commonly reported catalyst/ligand/base systems,[14] the widely used combination of PdCl$_2$(dppf) catalyst with Ph$_3$As ligand and Cs$_2$CO$_3$ as a base (procedure B) emerged as the only case where coupling was

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(1) (a) Berckmoes, K.; De Clercq, P. J. *J. Am. Chem. Soc.* **1995**, *117*, 5857. (b) Zhou, S.; Sey, M.; De Clercq, P. J.; Milanesio, M.; Viterbo, D. *Angew. Chem., Int. Ed.* **2000**, *16*, 2861.

(2) For a review, see: (a) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189. (b) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812.

(3) For reviews of some elegant syntheses in which this enzymatic reaction is mimicked, see: (a) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730. (b) Barrero, A. F.; Quílez del Moral, J. F.; Sánchez, E. M.; Arteaga, J. F. *Eur. J Org. Chem.* **2006**, 1627.

(4) Pd-catalyzed Negishi reaction of alkylzinc reagents with 1-haloalkenes: Negishi, E.; Liou, S. Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, *4*, 261.

(5) Cu-catalyzed reaction of alkenyl Grignard reagents with primary alkyl halides: Cahiez, G.; Chaboch, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733.

(6) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Org. Chem.* **1989**, *111*, 314.

(7) For a review, see: Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544.

(8) Stereoselectively prepared via Zr-catalyzed *syn*-carboalumination reaction of a terminal alkyne: Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.

(9) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.

(10) The enantiomeric excess of the intermediate diol **4** was found to be 96%, as determined via ^{1}H NMR analysis of the derived (2S)-methoxyphenylacetic esters.

(11) Compound **10** was prepared with 91% ee (GC), using a procedure first reported in: Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.

(12) A full discussion of this rather lengthy sequence is beyond the main focus of this communication. A scheme is included in the Supporting Information with detailed experimental procedures and spectral data.

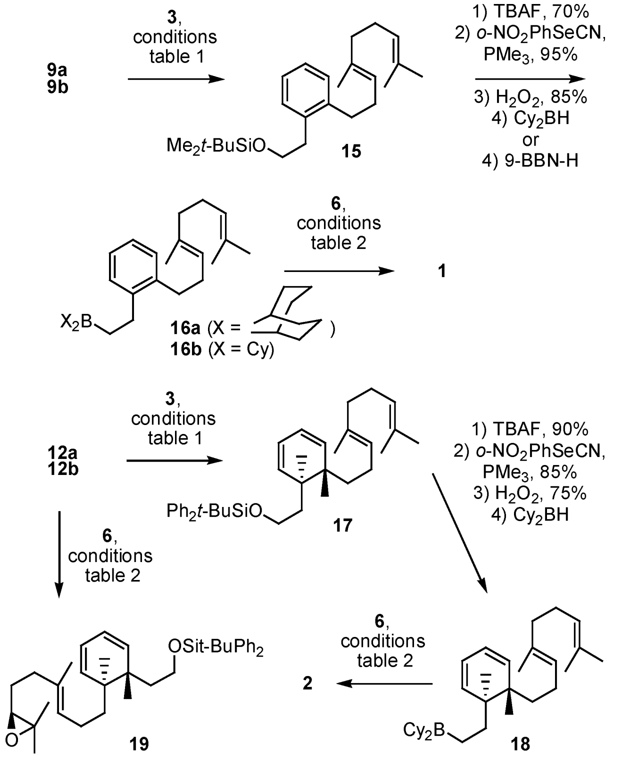
(13) Krief, A.; Laval, A. M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 869 and references therein.

observed, albeit in very low yield (entry 3). Prolonged heating only led to a complex reaction mixture.

Johnson and Braun have reported that *B*-alkyl Suzuki−Miyaura cross-coupling can be effected at room temperature when Cs_2CO_3 is used as a base (procedure B).[15] Here, this mild procedure led to a clean coupling reaction with acceptable yield (entry 4). The only detected side product was a homodimeric species arising from head-to-head coupling of the electrophile **3**. Therefore, more electrophile was added to the reaction after the initial iodoalkene was consumed. Thus, a significant increase in yield was achieved (entry 5). These optimized conditions gave similar results for the aromatic substrate **9b** (entry 6).

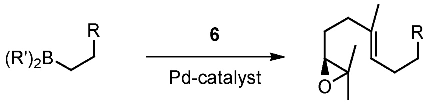
The further synthesis of epoxypolyenes **1** and **2** is delineated in Scheme 4. Deprotection and Grieco−Sharpless elimination of silyloxypolyenes **15** and **17**, followed by hydroboration, gave the *B*-alkylboron reagents **16a**,**b** and **18**. At this stage, we focused on coupling the more challenging electrophile **6**. The outcome is summarized in Table 2.

Scheme 4



We were pleased to note that the we could obtain epoxypolyene **1** even under the harsher conditions (entry 1, Table 2). As expected, no reaction occurred with the less reactive boron reagent **12a** (entry 2). The latter species did cross-couple with **6** using procedure B (entry 3), but surprisingly, the major reaction product was the coupled compound **20**, in which the conjugated diene was reduced (Scheme 5).[16]

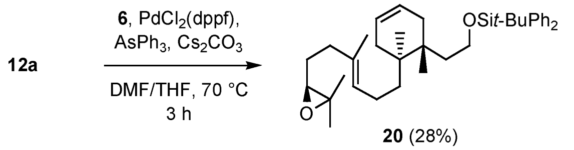
Table 2. Cross-Coupling Reactions of Some *B*-Alkylboron Compounds with **6** under Various Conditions



entry	substrate	product	procedure[a]	temp (°C)	time (h)	yield[b] (%)
1	**16a**	**1**	A	60	3	35
2	**12a**	**19**	A	60	3	0
3	**12a**	**19**	B	60	1	9[c]
4	**12b**	**19**	B	60	1	25
5	**12b**	**19**	B	60	3	10[d]
6	**12b**	**19**	B	rt	24	55
7	**12b**	**19**	B[e]	rt	20 + 20[e]	35
8	**12b**	**19**	B	rt	18[f]	70[g]
9	**16b**	**1**	B	rt	20[f]	45[g]
10	**18**	**2**	B	rt	16[f]	50[g]

[a] Reactions were conducted by adding 1.0 equiv of freshly prepared *B*-alkylboron reagent in THF/H_2O to (i) a stirred solution of 0.96 equiv of **6**, 0.10 equiv of $PdCl_2(PPh_3)_2$, and 2.0 equiv of 3 M K_3PO_4 in DMF (procedure A) or (ii) a stirred suspension of 0.96 equiv of **6**, 0.10 equiv of $PdCl_2(dppf)$, 0.10 equiv of Ph_3As, and 2.0 equiv of Cs_2CO_3 in DMF (procedure B). [b] Isolated yields after column chromatography. [c] Unexpected compound was isolated as major reaction product; see text for details. [d] Isolated with inseparable impurities from the complex reaction mixture. [e] Another 0.25 equiv of **6** was added during the course of the reaction. [f] Reaction worked up as soon as all of **6** was consumed. [g] See ref 18 for a general procedure.

Scheme 5



This unexpected reduction, however, did not occur when dicyclohexylborane derivative **12b** was coupled under the same conditions (entry 4).[17] The yield was still low and seemed to rapidly decrease upon longer reaction times (entry 5). In accordance with the earlier results for **3**, acceptable yields for the cross-coupling were achieved with the Johnson−Braun room temperature procedure (entry 6). Conversely, adding more electrophile with extended reaction times led to a significantly lower yield in this case (entry 7). This

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(14) Some common combinations of the bases NaOH, K_3PO_4, or Cs_2CO_3 with $Pd(PPh_3)_4$, $PdCl_2(dppf)$, or $PdCl_2(PPh_3)_2$ catalysts were tested in DMF or THF with or without extra ligands ($AsPh_3$ or PPh_3); see refs 6 and 7.

(15) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014.

(16) Similar problems have been reported regarding the unexpected reduction of a nitro group during Suzuki reaction with a 9-alkyl-9-BBN reagent; see: Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.

(17) This indicates the alkyl-9-BBN reagent as the hydride source for reduction, a process that has been described for dialkyl-9-BBN “ate” complexes: van Bergen, T. J.; Kellogg, R. M. *J. Am. Chem. Soc.* **1976**, *98*, 1964.

observation can be attributed to the expected limited stability of the assembled compounds under nucleophilic conditions. Optimal yields of epoxypolyenes were thus obtained by working up as soon as the epoxy iodoalkene **6** was consumed (entries 8−10, Table 2).[18]

In summary, the scope of the *B*-alkyl Suzuki−Miyaura cross-coupling reaction has been extended with a general way to assemble analogues of (3*S*)-oxidosqualene in a direct and stereoselective fashion. This approach offers a straightforward alternative to the established methods and excludes the need for possibly inconvenient organometallic reagents. Furthermore, this study clearly indicates dicyclohexylborane as the hydroboration reagent of choice. The required terminal alkenes are readily accessible via the reliable Grieco−Sharpless elimination of the corresponding primary alcohol.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including **11** and precursors thereof. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) General procedure for cross-coupling **6**: Under argon atmosphere, the terminal alkene substrate (1.0 mmol) was added to a freshly prepared slurry of dicyclohexylborane (1.5 mmol) in THF (4.8 mL) and stirred at 0 °C. Stirring was continued for 15 min at 0 °C and for 45−60 min without cooling. Upon completion, excess borane reagent was quenched with water (16 mmol, purged with argon). After stirring for 30 min at room temperature, the resulting clear solution was transferred via cannula to another reaction flask containing a stirred mixture of $PdCl_2$(dppf) (0.096 mmol), Ph_3As (0.096 mmol), Cs_2CO_3 (1.92 mmol), and **6** (0.96 mmol) in DMF (6.4 mL, purged with argon). The reaction was stirred in the dark at room temperature for 16−20 h. Upon complete consumption of **6**, saturated aqueous NaCl solution was added, and the aqueous phase was extracted with pentane/ether (1:1). The combined organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, ethyl acetate in *iso*-octane) to afford the pure coupled epoxypolyene (0.45−0.70 mmol).