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Synthesis of Amphidinolide E C10−C26 Fragment

Jorge Esteban, Anna M. Costa,* and Jaume Vilarrasa*

Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, Av. Diagonal 647, 08028 Barcelona, Catalonia, Spain

amcosta@ub.edu; jvilarrasa@ub.edu

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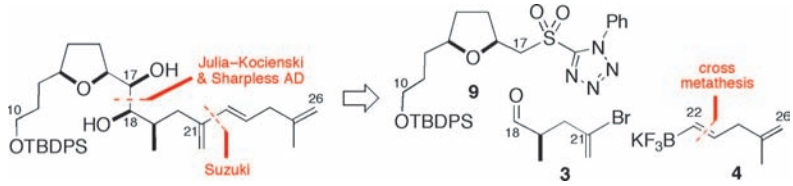
ABSTRACT



The key C10−C26 fragment in a total synthesis of (−)-amphidinolide E has been prepared from an oxolane-containing C10−C17 segment (9, derived from L-glutamic acid) via a Julia−Kocienski reaction with aldehyde 3, followed by a Sharpless AD to obtain the desired diol. The C22−C26 fragment was installed by means of an efficient Suzuki−Molander coupling, with an organotrifluoroborate reagent (4, arising from a cross-metathesis reaction between a vinylboronate and 2-methyl-1,4-pentadiene).

Amphidinolides are a family of cytotoxic marine natural products with diverse structures, isolated from Okinawa dinoflagellates (*Amphidinium* sp.).[1] Years ago we embarked on a project aimed at synthesizing different amphidinolides.[2] Among them, amphidinolide E (**1**), which features a 19-membered macrolide with an embedded tetrahydrofuran ring, eight stereogenic C(sp^3) atoms, two conjugate diene units, and an unprecedented side chain (which looks like a monoterpene unit at first sight but contains 11 carbons)[3] and exhibits a strong activity in vitro against murine lymphoma L1210. Its absolute stereochemistry was not established until 2002,[3b] when further amounts of sample became available through repeated cultivation. In short, amphidinolide E was and is an attractive target molecule.[4,5] We report an approach to amphidinolide E very different from those described to date,[4,5] which relies on a key C10−C26 fragment.

Our retrosynthetic analysis of **1** is shown in Scheme 1. Reasonable, standard disconnections at C9−C10 and C1−O bonds reveal two major segments.[6] The NE fragment, which is the subject of this communication, can be derived from the coupling of a synthon of type **2** with aldehyde **3** via a Julia−Kocienski reaction (henceforward, J−K reaction),[7] followed by an appropriate dihydroxylation of the C17−C18 double bond. Afterward, a C(sp^2)−C(sp^2) coupling, e.g., involv-

(1) Very recent reviews: (a) Kobayashi, J.; Kubota, T. *J. Nat. Prod.* **2007**, *70*, 451. (b) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77.

(2) (a) Mas, G.; González, L; Vilarrasa, J. *Tetrahedron Lett.* **2003**, *44*, 8805 (amphi K C1−C5 chiral blocks). (b) Andreou, T.; Costa, A. M.; Esteban, L.; González, L.; Mas, G.; Vilarrasa, J. *Org. Lett.* **2005**, *7*, 4083 (amphi K C9−C22 fragment). (c) Rodríguez-Escrich, C.; Urpí, F.; Vilarrasa, J. submitted for publication (amphi X total synthesis). (d) Rodríguez-Escrich, C.; Olivella, A.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2007**, *9*, 989 (amphi X/Y C12−C21 segments). (e) Esteban, J.; Costa, A. M.; Gómez, A.; Vilarrasa, J. *Org. Lett.* **2008**, *10*, 65 (amphi E C1−C5 chiroblocks). (f) Esteban, J. Ph.D. Thesis in process (2005−2008).

(3) (a) Kobayashi, J.; Ishibashi, M.; Murayama, T.; Takamatsu, M; Iwamura, M.; Ohizumi, Y.; Sasaki, T. *J. Org. Chem.* **1990**, *55*, 3421. (b) Kubota, T.; Tsuda, M.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 1651.

(4) Total syntheses: (a) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019. (b) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960. For diastereomers of amphidinolide E, see: (c) Va, P.; Roush, W. R. *Org. Lett.* **2007**, *9*, 307. (d) Va, P.; Roush, W. R. *Tetrahedron* **2007**, *63*, 5768.

(5) For syntheses of segments, see: (a) Marshall, J. A.; Schaaf, G.; Nolting, A. *Org. Lett.* **2005**, *7*, 5331 (C6−C21). (b) Heitzman, C. L.; Lambert, W. T.; Mertz, E.; Shotwell, J. B.; Tinsley, J. M.; Va, P.; Roush, W. R. *Org. Lett.* **2005**, *7*, 2405 (C6−C21). (c) Gurjar, M. K.; Mohapatra, S.; Phalgune, U. S.; Puranik, V. G.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 7899 (C12−C26).

(6) Two approaches were envisaged by us at the very beginning of this project (ref 2f) for the key steps: (i) a macrolactonization under the mildest possible conditions (to avoid epimerization at C2) as the last step, after a J−K reaction (C9−C10 bond); (ii) a ring-closing metathesis under appropriate conditions in the final step, after the ester formation.

(7) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26. For reviews, see: (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (c) Plesniak, K.; Zarecki, A.; Wicha, J. *Top. Curr. Chem.* **2007**, *275*, 163.

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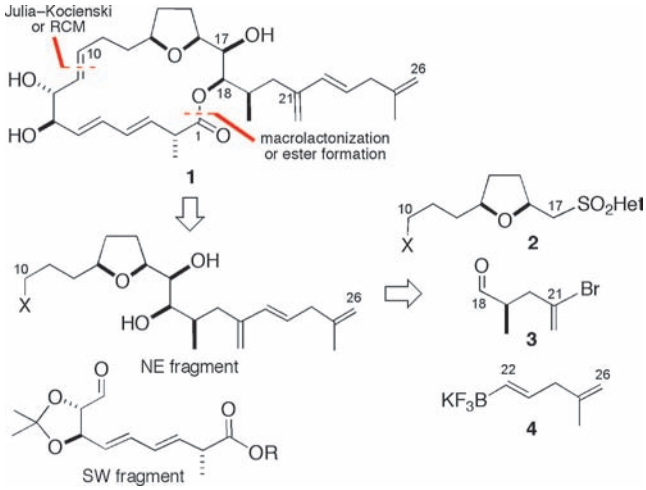
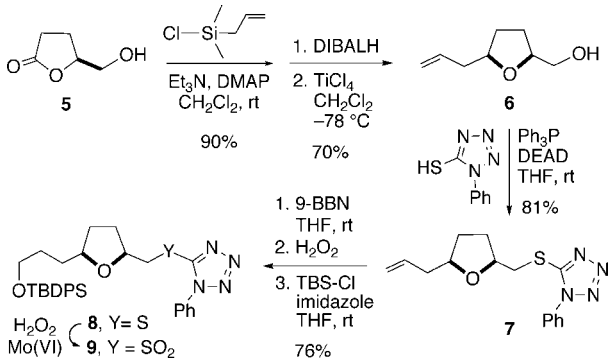
Scheme 1. Retrosynthetic Analysis of Amphidinolide E (**1**)



ing organotrifluoroborate **4**, could create the C21−C22 bond. Several challenges were inherent in this strategy. Moreover, its versatility (which should afford series of stereoisomers for future screenings) encouraged us to go ahead with the initial project,[2f] despite the publication of other syntheses.[4]

The synthesis of the C10−C17 fragment (see Scheme 2)

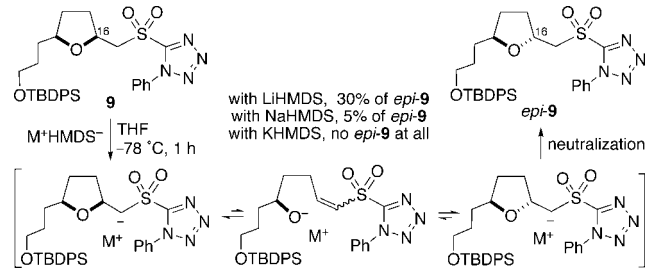
Scheme 2. Synthesis of Fragment C10−C17 (**9**)



began from butyrolactone **5** (commercially available or readily prepared from L-glutamic acid).[8] By means of a known intramolecular allylation (from the *O*-silyl derivative to the $TiCl_4$-generated oxocarbenium ion), the desired 2,5-disubstituted oxolane was obtained as a 85:15 *cis*−*trans* mixture.[9] Separation by chromatography furnished **6** in ca. 50% overall yield from **5**. Thioether **7** was then obtained under standard conditions (a Mitsunobu reaction with 1-phenyltetrazole-5-thiol as the nucleophile).[7] Anti-Markovnikov hydration of the double bond via hydroboration followed by oxidation with H_2O_2, protection of the resulting alcohol as its *tert*-butyldiphenylsilyl (TBDPS) ether (see **8**), and quantitative oxidation of the sulfide to the sulfone, with H_2O_2 and catalytic amounts of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ in EtOH at room temperature,[10] afforded **9** in 76% overall yield from **7** (around 30% from **5**). Compound **9** is equivalent to synthon **2**. As X of **2** may be Het′S or Het′SO_2 (a heteroaromatic sulfone different from SO_2Het of Scheme 1), the approach should allow us to carry out independent Julia−Kocienski reactions to link C17 and C18 and, later, C9 and C10.

With **9** in our hands, we turned our attention to its J−K reaction with aldehyde **3**.[11] Although β-alkoxysulfonyl-phenyltetrazoles have been utilized in some cases,[7b,c,12] a β-elimination reaction from the anionic intermediate and/or a scarce stereoselectivity are always possible.[13] To examine this transformation in our particular case, we first tested the stability of **9** under the conditions of the J−K reaction. When **9** was treated with LiHMDS in THF at −78 °C for 1 h and then the solution was quenched by pouring it into aqueous NH_4Cl at 0 °C, a 70:30 mixture of **9** and its epimer at C16 (*epi*-**9**) was recovered; that is, 30% epimerization occurred (Scheme 3). Conversely, under identical conditions with

Scheme 3. Configurational Stability of Alkaline Salts of **9**



NaHMDS or KHMDS, **9** was recovered almost or fully unchanged, respectively.

The influence of the base and solvent on the *E*/*Z* ratio was also examined, on a model (an analogue of **9**, see Table 1).

As a solution of KHMDS (solid) in DMF/HMPA afforded the best *E*/*Z* ratio (entry 7), these conditions were applied to

(8) (a) Lehmann, J.; Pieper, B. *Tetrahedron: Asymmetry* **1992**, *3*, 1537. (b) Figadère, B.; Harmange, J.-C.; Laurens, A.; Cavé, A. *Tetrahedron Lett.* **1991**, *32*, 7539. (c) Also see ref 2b.

(9) Pilli, R. A.; Riatto, V. B. *Tetrahedron: Asymmetry* **2000**, *11*, 3675.

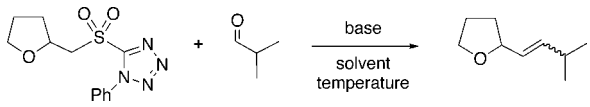
(10) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140.

(11) We prepared **3** from the Li enolate of *N*-propanoyl-4(*S*)-benzyloxazolidin-2-one and 2,3-dibromopropene. Its enantiomer is known: (a) Evans, D. A.; Kim, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 11323. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506.

(12) (a) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033. (b) Sivaramakrishnan, A.; Nadolski, G. T.; McAlexander, I. A.; Davidson, B. S. *Tetrahedron Lett.* **2002**, *43*, 213. (c) Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 12058. (d) Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 1081. (e) Chang, S.-K.; Paquette, L. A. *Synlett* **2005**, 2915. (f) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 769.

(13) (a) Smith, A. B., III; Brandt, B. M. *Org. Lett.* **2001**, *3*, 1685. (b) Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 4573. (c) Compostella, F.; Franchini, L.; Panza, L.; Prosperi, D.; Ronchetti, F. *Tetrahedron* **2002**, *58*, 4425. (d) Vicente, J.; Huckins, J. R.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 7258. (e) Miyashita, K.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M.; Imanishi, T. *J. Org. Chem.* **2008**, *73*, 5360.

Table 1. Screening the Conditions for the J−K Reaction of **9**

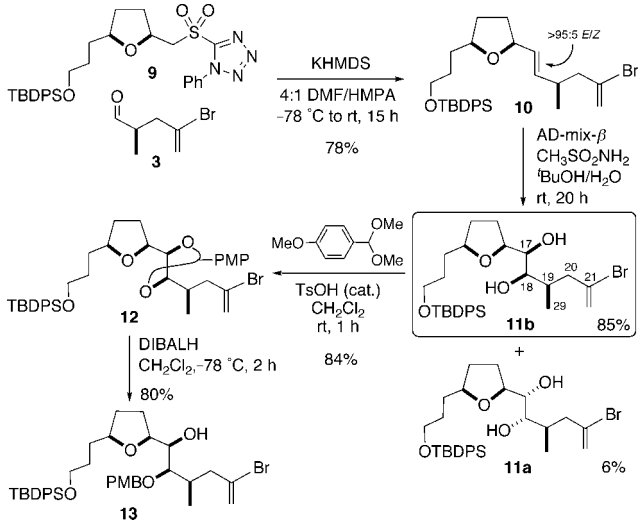


entry	base (soln), major solvent, temp[a]	*E*/*Z* ratio[b]
1	NaHMDS (in THF), THF, −78 °C to rt	15:85
2	NaHMDS (in THF), DME, −78 °C to rt	58:42
3	NaHMDS (in THF), DMF, −60 °C to rt	85:15
4	KHMDS (in toluene), THF, −78 °C to rt	60:40
5	KHMDS (in toluene), DME, −78 °C to rt	85:15
6	KHMDS (in toluene), DMF, −60 °C to rt	90:10
7	KHMDS (solid), 4:1 DMF/HMPA, −78 °C to rt	93:07

[a] The sulfone and base were mixed at −78 °C (or −60 °C, in some cases, to avoid freezing), for 10−15 min; after the addition of isobutyraldehyde and stirring for 1 h at the same temperature, the solution was allowed to warm up to rt for 2 h. [b] The *E*/*Z* ratios were determined by ^{1}H NMR analysis of the crude product mixtures.

the coupling of substrates **9** and **3**. To our delight, in this way **10** was obtained always in good yields and with excellent selectivities (>95:5 *E*/*Z*, Scheme 4).

Scheme 4. Synthesis and Dihydroxylation of **10**



The catalytic dihydroxylation of **10** with encapsulated OsO_4 (Os EnCat 40) and NMO in acetone/H_2O gave a 85% yield of two diols in a 2:1 ratio.[14] Sharpless asymmetric dihydroxylation[15] of **10** with AD-mix-α provided the same diols (**11a**/**11b**) in 97:3 ratio; a 93% yield of pure **11a** was isolated. We assumed that the configuration of **11a** was that shown in Scheme 4 on the basis of the well-established Sharpless empirical rule for the AD reaction of *trans*-disubstituted olefins (also see below).[15b] On the other hand, AD-mix-*β*, that is, the osmate−$(DHQD)_2PHAL$ complex,[15] and **10** gave a 7:93 **11a**/**11b** mixture, from which the desired diol **11b** was obtained in 85% yield after column chromatography (only this last reaction is shown in Scheme 4). Thus, these AD reactions took place with full regioselectivity—the CH_2═CBr moiety did not react at all—and excellent diastereofacial selectivity. Again, we relied upon the Sharpless empirical rule to attribute the configuration of the two newly created stereocenters of **11b**. The NMR coupling constants and a NOESY experiment agreed with the prediction and indicated that the main conformer of **11b** was that shown in Figure 1.[16]

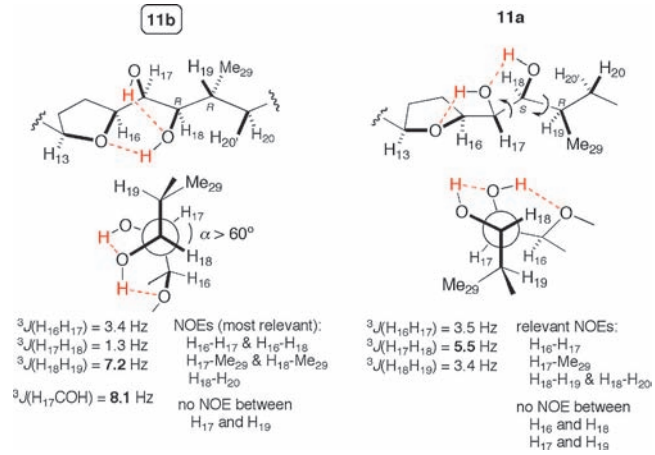


Figure 1. Relevant NMR data of **11b** and **11a** in $CDCl_3$.

For the sake of comparison, the main NMR data of **11a** are also included in Figure 1.[17]

The diol moiety of **11b** was protected as the acetal **12** (see Scheme 4, PMP = *p*-methoxyphenyl, ca. 1:1 mixture of epimers). We examined here if it would be possible, later, to deprotect selectively one of the hydroxy groups of the 1,2-diol moiety. Treatment of **12** with DIBALH gave rise to a very selective cleavage, as *p*-methoxybenzyl (PMB) ether **13** was isolated in 80% yield (91% brsm).[18]

Finally, organotrifluoroborate **4** was prepared by cross metathesis (CM) as shown in Scheme 5, namely, from

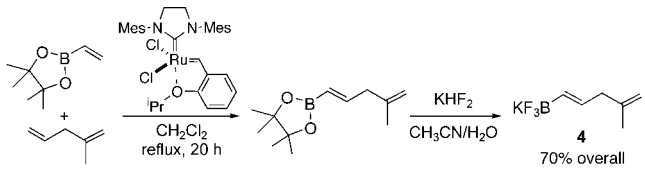
(14) According to the Kishi rule (Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247), they should be **11a** and **11b**, respectively.

(15) (a) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263. Very recent reviews: (b) Kolb, H. C.; Sharpless, K. B. In *Transition Metals for Organic Synthesis*; 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2, p 275. (c) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, 1725. (d) Français, A.; Bedel, O.; Haudrechy, A. *Tetrahedron* **2008**, *64*, 2495.

(16) See Supporting Information for the corresponding spectra. The largest HCCH coupling constant in the key moiety of **11b** indicates an almost antiperiplanar arrangement of H_{18} and H_{19}, whereas the very small gauche $^3J(H_{17}H_{18})$ suggests a dihedral angle closer to 90° than to 60° (see the Newman projection through the C18−C17 bond in Figure 1, left). The value of $^3J(H_{17}COH)$ is also worth noting. The most relevant NOEs agree with these observations (with H_{16}, H_{17}, H_{18}, Me_{29}, and H_{20} in the same, rear face). The depicted hydrogen bondings likely help to fix the conformation shown in Figure 1 (left).

(17) A full conformational study of this "byproduct" is outside the scope of our work. However, the $^3J(H_{17}H_{18})$ value for **11a**, the (small) cross peak between H_{16} and H_{17}, and the intense cross peak between H_{17} and Me_{29} may be accounted for by the main conformation depicted in Figure 1 (right); other possible minor rotamers (by counterclockwise 60° rotation of the C19−C18 bond and/or by clockwise rotation of the C18−C17 bond) cannot be ruled out.

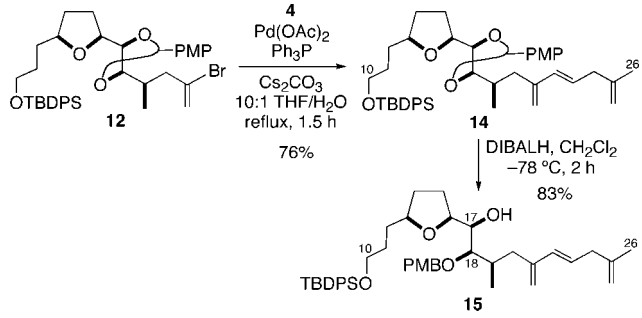
Scheme 5. Preparation of **4** via Cross Metathesis



commercially available vinylboronic acid pinacol ester,[19] 2-methyl-1,4-pentadiene (140 mol %), and the Hoveyda−Grubbs II initiator[20] (H−G II, only 2 mol %), to give the corresponding boronate, which was treated immediately with KHF_2 in 3:1 CH_3CN/H_2O to give **4**.[21] Salt **4** has not been reported to the best of our knowledge; it was isolated as a pale yellow powder, in 70% overall yield.[22]

The synthesis of fragment C10−C26 was completed as shown in Scheme 6. The Suzuki cross-coupling reaction

Scheme 6. Cross-Coupling Reaction of **12** and **4**



between **12** and **4** under the conditions of Molander et al.[23] afforded **14** (epimer mixture) in 76% yield.[24]

As expected (in the light of the conversion of **12** to **13**), the treatment of **14** with DIBALH gave the C18-OPMB-protected NE fragment (**15**) in 83% yield, with recovery of 10% of **14**. With AcOH/H_2O at room temperature, the cleavage of the acetal group of **14** was quick and practically quantitative to give the unprotected diol.[25]

We hope to report the assembly of appropriately substituted C10−C26 (NE) and C1−C9 (SW) fragments, as well as alternative but less successful routes to our NE segment(s), in a future full paper.

In conclusion, a fragment has been achieved that is key for our planned synthesis of **1** since both approaches[2f,6] go across this C10−C26 fragment. To obtain it in practical overall yields, a fine-tuning of some protocols to our case was essential. Thus, the J−K reaction(s) with the C10−C17 segment required an optimization, to avoid β-elimination and/or epimerization reactions and to attain the highest stereoselectivity during the formation of the C17−C18 double bond; with solid KHMDS in 4:1 DMF/HMPA, *E*/*Z* ratios equal to or higher than 20:1, without epimerization at all, have been achieved in all batches. On the other hand, AD-mix-β gave directly the desired dihydroxylation of this double bond, with excellent regioselectivity and diastereofacial selectivity. Regarding the C18−C26 triene moiety, among the methods examined by us to date the very efficient combination of a Grubbs CM (with only 2 mol % of H−G II, to prepare the boronate precursor of trifluoroborate **4**) with a Suzuki−Molander-type cross-coupling (of **4** with **12**) is remarkable.

Acknowledgment. Support from the Ministerio de Educación y Ciencia, through grants SAF2002-02728 and CTQ-2006-15393, is acknowledged. The Universitat de Barcelona contributed with a studentship to J.E. (from February 2004 till January 2008). Our group is a member of the IBUB (Institut de Biomedicina de la Universitat de Barcelona). Thanks are due to a reviewer for bringing to our attention ref 14.

Supporting Information Available: Experimental procedures, copies of the ^1H and ^{13}C NMR spectra of **7**, **8**, **9**, **10**, **11b**, **11a**, **13**, **4**, and **15**, and copies of 2D NMR spectra of **11b**, **11a**, **13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) The structure of **13** was assigned on the basis of 2D-NMR spectra (COSY, HSQC, and HMBC). Cross peaks between C18 and the methylene protons of OPMB ($^3J_{C-H}$) and between H_{17} and the OH proton ($^3J_{HH}$) are relevant. (b) The oxygen atom of the oxolane ring may play a role in this selective cleavage. We would have preferred the reverse cleavage, to obtain mainly the C17-OPMB isomer, saving two steps, since later we need C18-OH free (and, in principle, C17-OH protected).

(19) Several CM of this etheneboronate ester (2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane), with the Grubbs II reagent, have been reported: (a) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031 (and refs 13 and 14 therein). (b) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187. For other alkenylboronates, see: (c) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733.

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

(21) Very recent review of potassium organotrifluoroborates: Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288.

(22) Attempts to prepare **4** directly, from potassium trifluoro(vinyl)borate (ethenyltrifluoroborate, $KF_3BCH{=}CH_2$), 2-methyl-1,4-pentadiene, and H−G II, in refluxing CH_2Cl_2/acetone, were unsuccessful (no reaction).

(23) Five mole percent of $Pd(OAc)_2$, 10 mol % of PPh_3, and 300 mol % of Cs_2CO_3. See: (a) Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950. For an example in anhydrous THF, see: (b) Fürstner, A.; Larionov, O.; Flügge, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5545. For reviews, see: (c) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, *38*, 49. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275.

(24) The reaction of **12** and **4** (Scheme 6, ref 23) was complete within 1.5 h. Monoprotected diol **13** can be coupled with **4** in the same way, but the attempted coupling of unprotected diol **11b** led mainly to decomposition. For the sake of comparison, the coupling of **12** with the boronate of Scheme 5 was only partial even after overnight heating in a bath at 70 °C (as in Scheme 6), under the following conditions for the Suzuki−Miyaura reaction: $PdCl_2$(dppf) (10 mol %) and $Ba(OH)_2{\cdot}8H_2O$ (300 mol %) in DMF. Compare: (a) Gopalarathnam, A.; Nelson, S. G. *Org. Lett.* **2006**, *8*, 7. (b) Fürstner, A.; Nevado, C.; Waser, M.; Tremblay, M.; Chevrier, C.; Teply, F.; Aissa, C.; Moulin, E.; Müller, O. *J. Am. Chem. Soc.* **2007**, *129*, 9150. (c) Most recent review: Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013.

(25) Oxidative removal (e.g., with DDQ) of PMP and PMB groups is counterindicated as conjugate dienes are too sensitive; for an overview, see: Wutts, P. G. M.; Greene, T. W. *Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, 2007, p 124.