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Synthesis of enantiomerically pure vinylcyclopropylboronic esters via cross-metathesis

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Abstract

The potent antibiotic ambruticin caused us to investigate two new aspects of cyclopropylboronic ester chemistry: we established the analytical basics for all 1,2,3-trisubstituted diastereoisomers as well as the cross-metathesis as a tool to synthesise vinylcyclopropylboronic esters.

Keywords: Cyclopropanes; Boron; Diastereoselective synthesis; Zinc reagents; Metathesis

1. Introduction

Cyclopropylboronic esters have been shown to be versatile building blocks for cyclopropane chemistry by utilising the broad synthetic potential of the boron moiety [1–4]. Since the first successful reports about diastereoselective, auxiliary directed cyclopropanations of alkenylboronic esters by Imai et al. in 1990, [5] a number of improvements of the original sequence as well as new transformations of the products were reported [6–8]. The introduction of diol **1** [9] was a step toward stable, enantiomerically pure boronic esters **2** in general and toward cyclopropane derivatives **3** in particular (Fig. 1) [10–13]. The convenient handling of the intermediates allowed not only the separation of diastereoisomers, but also the straightforward manipulation of the side-chain (R). Of particular interest was the allyl derivative **4**: by carefully choosing the reaction conditions, either diastereoisomer **5a** or **5b** would be obtained [13]. In this contribution we would like to report an extension of the scope of such enantiomerically pure building blocks.

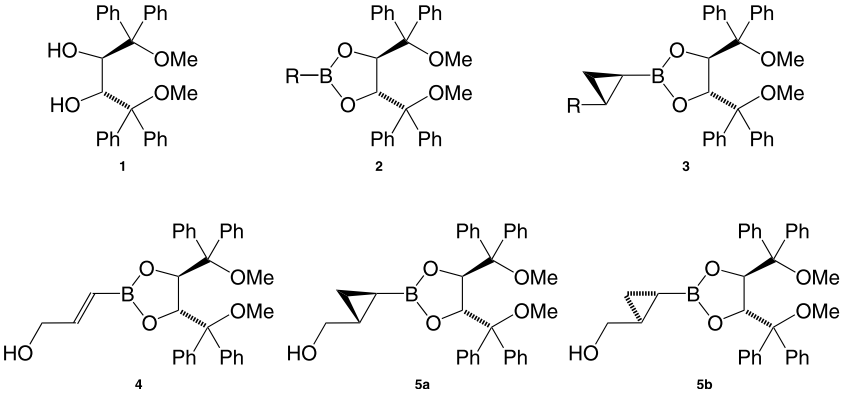

Fig. 1. Highly stable boronic esters of diol **1**.

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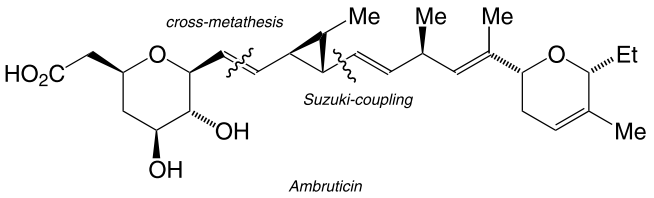
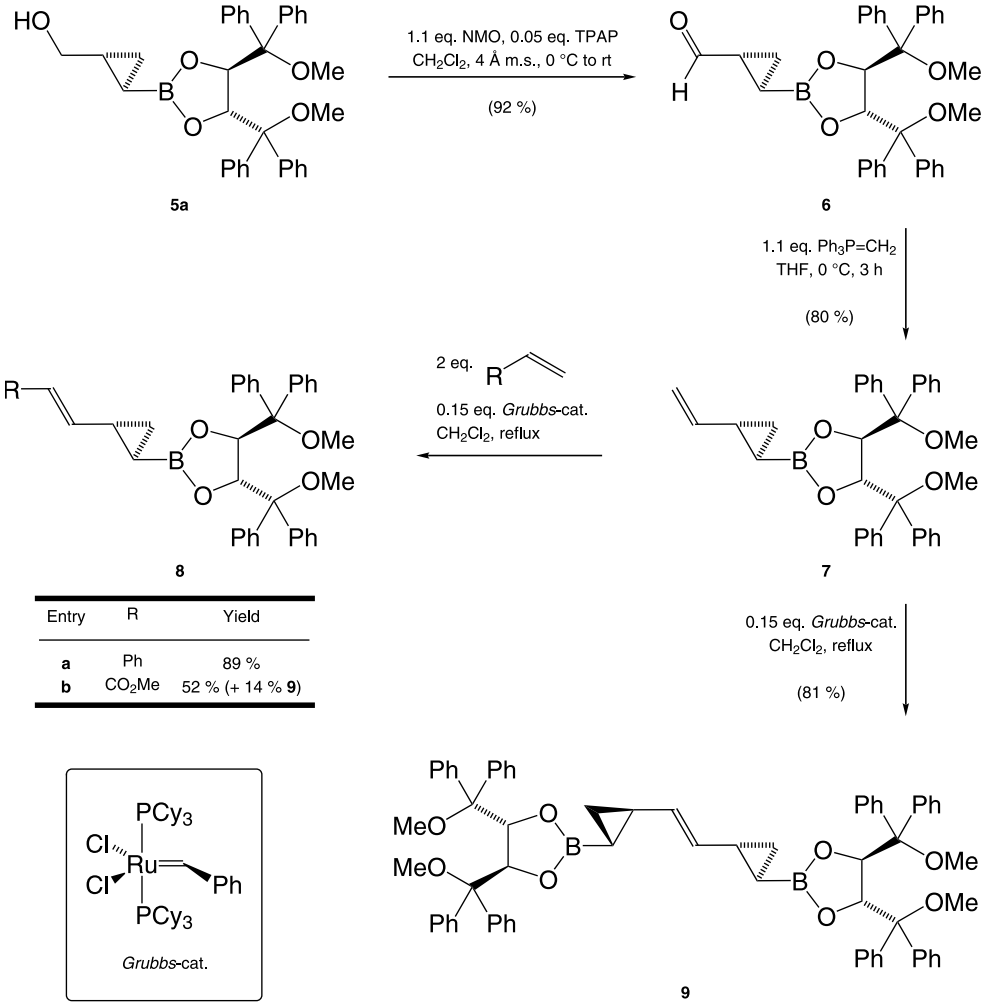


Fig. 2. Restrosynthesis of the potent antibiotic ambruticin.

We were especially intrigued by the structural aspects of the potent antibiotic ambruticin (Fig. 2) [14–17]: for the 1,2-divinyl-substituted cyclopropane it would be ideal to use suitable cyclopropylboronic esters as key intermediates [18]. The well documented fact that *Suzuki*-couplings can be employed to synthesise vinylcyclopropanes [11,19] allows a convenient retrosynthetic disconnection. The second *E*-double-bond was envisaged to stem from a cross-metathesis, a reaction that was recently shown to be applicable to allylboronic esters [20]. Initially, we would need to establish two features: (a) cyclopropylboronic esters such as diastereoisomer **5a** can be converted to vinylcyclopropanes that in turn would need to be suitable substrates for a cross-metathesis; and (b) cyclopropanation of alkenylboronic ester **4** should not only lead to 1,2-disubstituted cyclopropanes, but also higher substituted derivatives. Both questions are addressed in this communication.

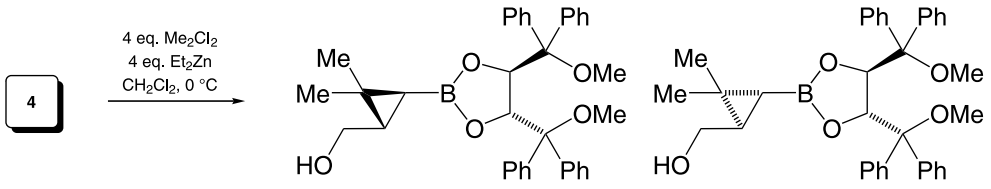
2. Results and discussion

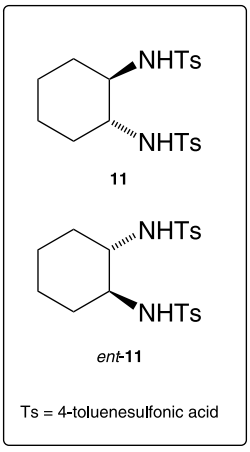
The oxidation of the primary alcohol **5a** to aldehyde **6** was conveniently performed by using Ley's conditions [21], while the following Wittig-reaction [22] led to vinylcyclopropane (**7**) in good overall yield (Scheme 1). With this simple sequence, the starting material for our first investigation can be obtained in multigram scale. Although the cross-metathesis between **7** and styrene was sluggish, the corresponding *E*-olefin **8a** was obtained in high yield[23]. With the standard Grubbs-catalyst [24,25] no *Z*-product was detected. This holds also true for electron-deficient olefins such as methyl acrylate, but the reaction proved to be much slower and



Entry	R	Yield
a	Ph	89 %
b	CO_2Me	52 % (+ 14 % **9**)

Scheme 1.





Entry	mmol **4**/ml CH_2Cl_2	Additive	Conversion	d.r. (**10a**:**10b**)
1	0.025	none	41 %	88:12
2	0.040	none	45 %	76:24
3	0.040	**11**	30 %	80:20
4	0.040	*ent*-**11**	39 %	81:19
5	0.020	none	90 %[a]	69:31

[a] The addition of 4 eq. of the reagents was repeated three times.

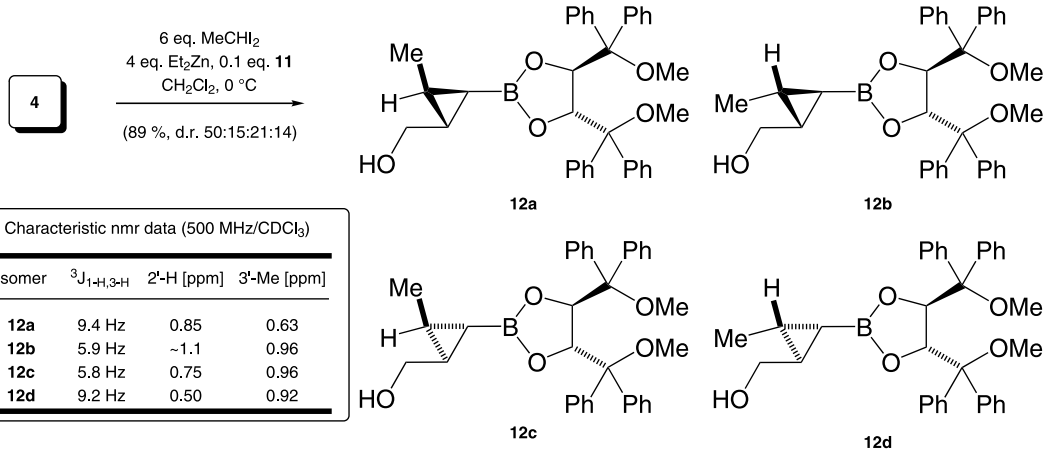
Characteristic nmr data (500 MHz/$CDCl_3$):

Compound	2'-H [ppm]	3'-H_{trans}	3'-Me_{trans}	3'-Me_{cis}
5a	1.00	0.06	-	-
5b	0.64	0.41	-	-
10a	0.87	-	0.58	0.90
10b	0.58	-	0.87	0.92

Scheme 2.

as a side-product to **8b** the dicyclopropylethylene (**9**) was isolated in 14% yield. It is interesting to note that in the absence of a second olefin this side-reaction led exclusively to compound **9** (81% yield), a versatile intermediate.

Next we examined the possibility to synthesise higher substituted cyclopropylboronic esters starting from allyl alcohol **4**. We thought to investigate Simmons-Smith-type cyclopropanations with 2,2-diiodopropane [26] and diethylzinc [27] and hoped to obtain the diastereoisomeric cyclopropanes **10a** and **10b**. While the zinc reagent proved to be highly reactive and fast decomposition could be observed, the sterically demanding auxiliary hampered the successful transformation (Scheme 2): The conversion was low regardless whether the concentration was altered or an additive such as bissulfonamide (**11**) or *ent*-**11** [11,28,29] was present. Only a slight impact on the diastereoisomeric ratio was observed, however, a lower concentration of olefin **4** in dichloromethane would seem to favour the selectivity. In order to get an increased conversion a repeated addition of reagents was essential. In view of the forthcoming transformations to 1,2,3-trisubstituted cyclopropylboronic esters it was imperative to assign the configuration of **10a** and **10b** via characteristic NMR data. We had previously demonstrated that the 2′-H and 3′-H_{trans} protons are the most telling signals for 1,2-disubstituted cyclopropylboronic esters such as **5a** and **5b**. The corresponding 2′-H signals for **10a** and **10b** show similar characteristic chemical shifts. In addition, the 3′-methyl



Characteristic nmr data (500 MHz/$CDCl_3$)

Isomer	$^3J_{1\text{-}H,3\text{-}H}$	2'-H [ppm]	3'-Me [ppm]
12a	9.4 Hz	0.85	0.63
12b	5.9 Hz	~1.1	0.96
12c	5.8 Hz	0.75	0.96
12d	9.2 Hz	0.50	0.92

Scheme 3.

signals follow the same trend as the 3′-H protons: While the chemical shifts of the methyl-groups in *cis*-position to the 1′-H protons are not expressive, the groups in *trans*-position are significantly different for the two diastereoisomers. The NMR assignment was further supported by the fact that the preferred facial attack of the double-bond by the zinc carbenoids was for both types of cyclopropanations the same.

The reactivity of the zinc reagent obtained from 1,1-diiodoethane [30] and diethylzinc [31,32] proved to be high as well, and fortunately the conversion of alkenylboronic ester **4** to cyclopropanes **12** was significantly faster—especially in the presence of bissulfonamide **11**; cyclopropylboronic esters **12a**–**d** were obtained in 89% yield within 21 h (Scheme 3). The complex diastereoisomeric mixture (**12a**–**12b**–**12c**–**12d** in a 50:15:21:14 ratio) could not be fully separated, but the significant NMR signals were conveniently assigned. Moreover, we were pleased to find that the minor diastereoisomer **12d** could be separated by mplc, an essential preliminary result for our envisaged ambruticin synthesis: Intermediate **12d** should be readily available via the palladium catalysed decomposition of diazoethane [18]. The following NMR assignment (configuration of **12a**–**d**) will be the key to further projects on 1,2,3-trisubstituted cyclopropylboronic esters. The relative configuration C1–C3 was unproblematic since the coupling constants $^{3}J_{1\text{-H},3\text{-H}}$ show a *trans*- (5.8/5.9 Hz) and a *cis*-relationship (9.4/9.2 Hz), respectively. The relative ^{1}H-NMR shifts of the 3′-methyl groups were also diagnostic, because a direct comparison with compounds **10a** and **10b** already allowed the assignment of **12a** (and with this indirectly of **12d**). The result was confirmed by the characteristic down-field shift (**12a** relative to **12d**) of the 2′-H protons. The same reasoning also led to the assignment of boronic esters **12b** and **12c** (relative down-field shift of the 2′-H proton).

In summary, we have synthesised vinylcyclopropylboronic esters via a cross-metathesis for the first time, and could also demonstrate that a variation of the Simmons–Smith reaction allowed the synthesis of tri- as well as tetrasubstituted cyclopropylboronic esters. The NMR assignment of the absolute configuration of all new cyclopropanes were a crucial first step toward an envisaged synthesis of the antibiotic ambruticin.

Acknowledgements

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References

[1] D.S. Matteson, in: K. Hafner, C.W. Rees, B.M. Trost, J.-M. Lehn, P. von Ragué Schleyer (Eds.), Stereodirected Synthesis with Organoboranes, Springer-Verlag, Heidelberg, 1995.
[2] A. Pelter, K. Smith, H.C. Brown, Borane Reagents, Academic Press, London, 1988.
[3] A. Suzuki, J. Organomet. Chem. 576 (1999) 147.
[4] D.S. Matteson, Tetrahedron 54 (1998) 10555.
[5] T. Imai, H. Mineta, S. Nishida, J. Org. Chem. 55 (1990) 4986.
[6] J. Pietruszka, M. Widenmeyer, Synlett (1997) 977.
[7] (a) S.M. Zhou, M.Z. Deng, L.J. Xia, M.H. Tang, Angew. Chem. 110 (1998) 3061;
(b) S.M. Zhou, M.Z. Deng, L.J. Xia, M.H. Tang, Angew. Chem. Int. Ed. 37 (1998) 2845.
[8] J. Pietruszka, T. Wilhelm, A. Witt, Synlett (1999) 1981.
[9] K. Nakayama, J.D. Rainier, Tetrahedron 46 (1990) 4165.
[10] J.E.A. Luithle, J. Pietruszka, Liebigs Ann./Recueil (1997) 2297.
[11] J.E.A. Luithle, J. Pietruszka, J. Org. Chem. 64 (1999) 8287.
[12] J.E.A. Luithle, J. Pietruszka, Eur. J. Org. Chem. (2000) 2557.
[13] J.E.A. Luithle, J. Pietruszka, J. Org. Chem. 65 (2000) 9194.
[14] S.M. Ringel, R.C. Greenough, S. Roemer, D. Conner, A.L. Gutt, B. Bair, G. Kanter, M.V. Strandtmann, J. Antibiot. 30 (1977) 371.
[15] A.S. Kende, Y. Fujii, J.S. Mendoza, J. Am. Chem. Soc. 112 (1990) 9645.
[16] A.S. Kende, J.S. Mendoza, Y. Fujii, Tetrahedron 49 (1993) 8015.
[17] (a) E. Lee, S.J. Choi, H. Kim, H.O. Han, Y.K. Kim, S.J. Min, S.H. Son, S.M. Lim, W.S. Jang, Angew. Chem. 114 (2002) 184;
(b) E. Lee, S.J. Choi, H. Kim, H.O. Han, Y.K. Kim, S.J. Min, S.H. Son, S.M. Lim, W.S. Jang, Angew. Chem. Int. Ed. 41 (2002) 176.
[18] I.E. Markó, T. Kumamoto, T. Giard, Adv. Synth. Catal. 344 (2002) 1063.
[19] S.-M. Zhou, Y.-L. Yan, M.-Z. Deng, Synlett (1998) 198.
[20] (a) S.D. Goldberg, R.H. Grubbs, Angew. Chem. 114 (2002) 835;
(b) S.D. Goldberg, R.H. Grubbs, Angew. Chem. Int. Ed. 41 (2002) 807.
[21] S.V. Ley, J. Norman, W.P. Griffith, S.P. Marsden, Synthesis (1994) 639.
[22] N.J. Lawrence, The Wittig reaction and related methods, in: J.M.J. Williams, C.J. Moody (Eds.), Preparation of Alkenes. A Practical Approach, Oxford University Press, Oxford, UK, 1996, p. 19.
[23] Representative data for compound **8a**: $[\alpha]_{D}^{21} = -77$ ($c = 0.4$, $CHCl_3$); softening range: 89–93 °C; ^{1}H-NMR data (500 MHz, $CDCl_3$) δ (ppm) = −0.32 (ddd, $^{3}J_{1',2'} = 9.9$, $^{3}J_{1',3'a} = 6.6$, $^{3}J_{1',3'b} = 5.2$ Hz, 1H, 1′-H), 0.39 (ddd, $^{3}J_{2',3'a} = 7.7$, $^{3}J_{1',3'a} = 6.7$, $^{3}J_{3'a,3'b} = 3.5$ Hz, 1H, 3′-H$_a$), 0.52 (ddd, $^{3}J_{2',3'b} = 9.9$, $^{3}J_{1',3'b} = 5.1$, $^{3}J_{3'a,3'b} = 3.5$ Hz, 1H, 3′-H$_b$), 1.47–1.52 (m, 1H, 2′-H), 3.01 (s, 6H, OC*H*$_3$), 5.29 (s, 2H, 4-H/5-H), 5.51 (dd, $^{3}J_{1'',2''} = 15.7$, $^{3}J_{2',1''} = 8.9$ Hz, 1H, 1″-H), 6.36 (d, $^{3}J_{1'',2''} = 15.7$ Hz, 1H, 2″-H), 7.14–7.37 (m, 25H, arom.-H); ^{13}C-NMR data (125 MHz, $CDCl_3$) δ (ppm) = 2.8 (C-1′); 13.2 (C-2′); 21.8 (C-3′); 51.7 (CPh_2OCH_3); 77.5 (C-4/C-5); 83,2 (CPh_2OCH_3); 125.5, 126.5, 127.2, 127.3, 127.5, 127.8, 128.3, 128.4 (arom. *C*H), 129.7 (C-1″), 134.6 (C-2″), 137.7, 141.1, 141.2 (arom. C_{ipso}).
[24] P. Schwab, R.H. Grubbs, J.W. Ziller, J. Am. Chem. Soc. 118 (1996) 100.

[25] T.R. Belderrain, R.H. Grubbs, Organometallics 16 (1997) 4001.
[26] A. Pross, S. Sternhell, Aust. J. Chem. 23 (1970) 989.
[27] A.B. Charette, N. Wilb, Synlett (2002) 176.
[28] H. Takahashi, T. Kawakita, M. Ohno, M. Yoshioka, S. Kobayashi, Tetrahedron 48 (1992) 5691.
[29] S.E. Denmark, S.P. O'Connor, J. Org. Chem. 62 (1997) 584.
[30] E.C. Friedrich, S.N. Falling, D.E. Lyons, Synth. Commun. 5 (1975) 33.
[31] S.E. Denmark, B.L. Christenson, S.P. O'Connor, N. Murase, Pure Appl. Chem. 68 (1996) 23.
[32] (a) A.B. Charette, J. Lemay, Angew. Chem. 109 (1997) 1163; (b) A.B. Charette, J. Lemay, Angew. Chem. Int. Ed. Engl. 36 (1997) 1090.