Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 61 (2005) 4427–4436
Tetrahedron

Enantioselective total synthesis of (−)-microcarpalide

Paolo Davoli,* Raffaele Fava, Stefania Morandi, Alberto Spaggiari and Fabio Prati*

Dipartimento di Chimica, Università di Modena e Reggio Emilia, via Campi 183, I-41100 Modena, Italy

Received 8 December 2004; revised 10 February 2005; accepted 24 February 2005

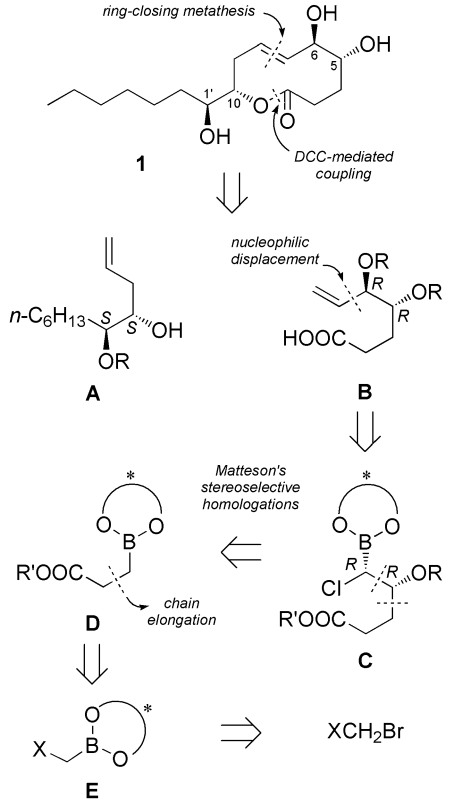
Available online 17 March 2005

Abstract—The enantioselective total synthesis of the actin-targeting metabolite (−)-microcarpalide is described. Key steps include ring-closing metathesis (RCM) for the final construction of the 10-membered lactone framework and stereoselective homologation of boronic esters for the insertion of all stereocentres with the desired absolute configuration. In particular, the acidic fragment was prepared in seven steps from a suitable chiral bromomethane boronate by means of two sequential stereoselective homologations to install the two stereocentres with the correct final *R* stereochemistry, employing (−)-pinanediol as the chiral director. Subsequent elaboration to the required C_7 backbone entailed nucleophilic displacement with a vinyl Grignard reagent, oxidative cleavage of the boronic scaffold and protection–deprotection manipulations. Interestingly, when the tribenzyloxy diene ester resulting from DCC-mediated coupling of the two key synthons was subjected to RCM in the presence of Grubbs' catalyst, the reaction proceeded stereoselectively to yield the desired *trans* oxecin-2-one, albeit with poor conversion.

1. Introduction

Actin-targeting small molecules are currently receiving an increasing interest as potential lead structures for the development of new therapeutic agents. The organization of the actin cytoskeleton plays a prominent role in a variety of processes such as cell shape change, cell migration and, ultimately, tumor cell invasion and metastasis. Hence, compounds that are capable of interfering with actin dynamics may offer promising opportunities as novel anticancer drugs.[1]

Microcarpalide (**1**) is a novel alkyl-substituted nonenolide (Scheme 1) that was discovered from fermentation broths of an unidentified endophytic fungus isolated from *Ficus microcarpa* L. in the framework of a search campaign for new secondary metabolites with anticytoskeletal activity.[2] In particular, microcarpalide was found to display a remarkable disrupting action on actin microfilaments, while showing only weak toxicity to mammalian cells.[2] By virtue of such a peculiar biological activity, the apparently simple, but yet stereochemically demanding macrocyclic structure of this new fungal metabolite has aroused the interest of the chemical community, and a few total syntheses have appeared accordingly.[3–7]



Scheme 1. Retrosynthetic disconnections.

Keywords: Fungal metabolites; Nonenolides; Actin-targeting compounds; Microfilament disrupting activity; Asymmetric homologation; Boronic esters; Ring-closing metathesis.
* Corresponding authors. Tel.: +39 59 2055056; fax: +39 59 373543 (F.P.); e-mail: prati.fabio@unimore.it

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.02.069

In the course of our previous total synthesis of microcarpalide, we had successfully exploited Matteson's asymmetric homologation[8] to insert sequentially the two stereocentres at positions 10 and 1′ with the required *S* absolute configuration, using (+)-pinanediol as the chiral director.[5] Along this line, we reasoned that the two remaining stereocentres, namely 5*R* and 6*R*, could be also installed likewise by an enantioselective approach featuring the stereoselective homologation of suitable chiral boronic esters, rather than from the chiral pool.[3–6] Hence, a modified retrosynthetic route was devised, as outlined in Scheme 1.

Our synthetic strategy relied again on ring-closing metathesis (RCM)[9] for the final construction of the 10-membered unsaturated macrocycle, owing to the inherently convergent nature of this powerful transformation.[10] Accordingly, tactical disconnection of (−)-microcarpalide (**1**) into subunits **A**[5] and **B** was envisaged (Scheme 1).

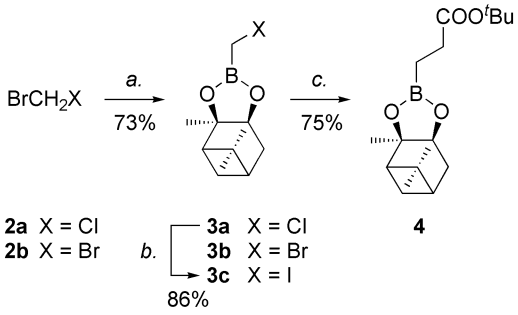
Retrosynthetically, the acidic fragment **B** can be ultimately deconvoluted to chiral boronate **E** (Scheme 1), which is easily obtained from the corresponding halobromomethane and (−)-pinanediol that serves as the chiral auxiliary of choice. In particular, chain elongation of **E** by means of a suitable lithium enolate should firstly provide C_3 boronic ester **D**, which would then undergo two consecutive stereoselective homologations in the presence of (dichloromethyl)lithium to afford α-chloro boronate **C** (Scheme 1). The stereochemical outcome of both homologation reactions would be controlled by (−)-pinanediol as the chiral director, which would induce the desired *R* absolute configuration at the newly inserted chlorine-bearing carbon atoms. Nucleophilic displacement by a vinyl Grignard reagent, followed by alkaline oxidative removal of the boronic scaffold and protection–deprotection manipulations, would finally result in the required C_7 terminal alkene **B** bearing two adjacent hydroxy groups in a *threo* fashion with the correct *R* stereochemistry (Scheme 1).

2. Results and discussion

2.1. Initial manouvre: synthesis of the C_3 unit

The enantioselective route to the C_7 fragment **B** began with the preparation of the appropriate chiral halomethaneboronate **3** which was required to build up the C_3 starting unit by nucleophilic displacement with the lithium enolate of *tert*-butylacetate.[11,12] For the carboxylic group, in particular, we envisaged that protection as a *tert*-butyl ester would be appropriate, owing to its well-known resistance to strongly basic environments such as those that were planned to be encountered in all the subsequent steps of our synthetic voyage, homologations included,[11,13,14] and because of great ease of deprotection.

Initial experiments were focused on exploring the performance of different halogen derivatives (**3a–c**) in the reaction with *tert*-butylacetate in the presence of LDA (Scheme 2).[11,12] Chloro derivative **3a** was prepared from bromochloromethane (**2a**) according to a literature procedure.[15] By close analogy, pinanediol bromomethaneboronate (**3b**) was



Scheme 2. (a) *n*-BuLi, THF, −78 °C, then $B(OMe)_3$, −78 °C, then TMSCl or TMSBr, −78 °C→rt, then (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol, rt; (b) NaI, acetone, rt (86%); (c) *tert*-butylacetate, LDA, THF, −78 °C.

readily synthesized in 73% overall yield by sequential treatment of dibromomethane (**2b**) with *n*-BuLi, trimethylborate[16] and trimethylbromosilane† in THF at −78 °C, followed by addition of (−)-pinanediol at rt.[12,15] Formation of the C–B bond was confirmed by a broad signal at 8.2 ppm in the ^{13}C NMR spectrum. In contrast, iodo analogue **3c** was obtained in 86% yield from **3a** by halogen exchange with sodium iodide in dry acetone (Scheme 2).[12,17] The presence of a new highfield signal (−22.8 ppm) in the ^{13}C NMR spectrum was suggestive of an iodine-bearing carbon atom,[18] which was confirmed by the correlation with the CH_2B protons in the COSY spectrum.

For the assembly of the C_3 unit, *tert*-butylacetate and halomethaneboronates **3a–c** were treated with LDA in THF at −78 °C (Scheme 2).[12] In the case of chloro derivative **3a**, only partial conversion was achieved and 2-[*tert*-butoxycarbonyl]ethaneboronate (**4**) was obtained in only 28% yield, along with *tert*-butylacetoacetate as the main reaction product arising from Claisen self-condensation of *tert*-butylacetate.[11] In contrast, most satisfactorily, reaction with bromomethaneboronate **3b** provided the displacement product **4** in 75% yield, whereas a slightly lower yield was observed with the iodo analogue **3c** (65%).

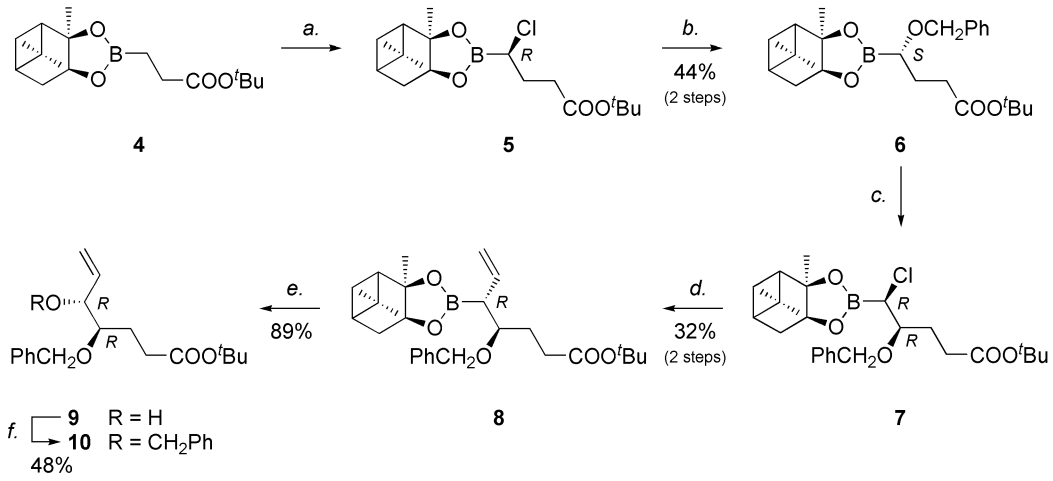
2.2. Asymmetric synthesis of the C_7 fragment

With a substantial amount of C_3 boronic ester **4** in hand, we set sails for the acidic C_7 fragment that was required for the assembly of the diene ester to be subsequently used in the RCM macrocyclization.

To this end, we devised applying two subsequent stereoselective homologations on chiral boronic ester **4** to install the two contiguous stereocentres with the required *R* absolute configuration, by analogy to the preparation of the alcoholic C_{11} fragment performed in the course of our previous total synthesis.[5] In the present case, however, (−)-pinanediol had to be used as the chiral director for the homologation reaction, since it is reported to induce the *R* absolute configuration at the newly formed stereocentre.[8,13]

Addition of in situ-generated (dichloromethyl)lithium to chiral *tert*-butoxycarbonyl boronate **4** at −100 °C in THF,[19]

† When trimethylchlorosilane was used instead,[15] products **3a** and **3b** were formed in a 1:1 ratio.



Scheme 3. (a) (Dichloromethyl)lithium, $ZnCl_2$, THF, −100 °C→rt; (b) benzyl alcohol, *n*-BuLi, THF, −78 °C→rt, then reflux (44% over two steps); (c) (dichloromethyl)lithium, $ZnCl_2$, THF, −100 °C→rt; (d) vinylmagnesium bromide, THF, −78 °C→rt (32% over two steps); (e) H_2O_2, NaOH, THF, 0 °C→45 °C (89%); (f) NaH, DMF, $PhCH_2Br$, −35 °C→−10 °C (48%).

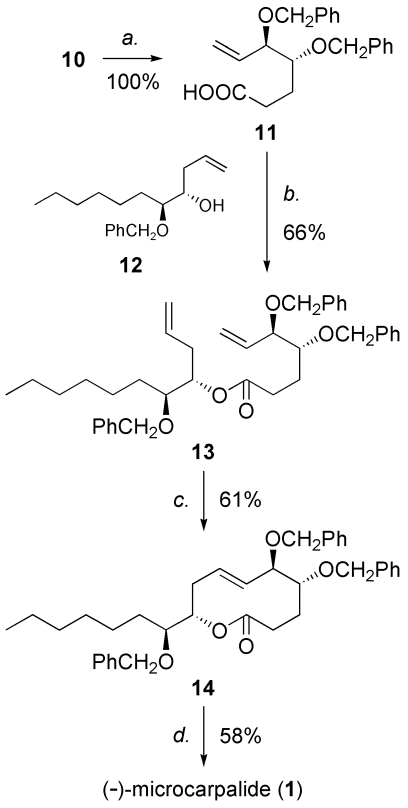
followed by treatment with zinc chloride (1 M solution in diethyl ether),[8,14] resulted in chain extension to α-chloro derivative **5** in 66% yield and diastereoisomeric excess greater than 98% (Scheme 3). Successful insertion of a Cl-bearing carbon atom into the carbon–boron bond was confirmed by a broad resonance at 43.7 ppm in the ^{13}C NMR spectrum; in addition, a doublet of doublets at 3.51 ppm accounting for the H-1 proton featured in the ^{1}H NMR spectrum. The diastereoselectivity of the homologation was determined by using the H_{endo} proton of the pinanyl moiety (1.17 ppm, doublet) as diagnostic marker,[13] as already reported.[5] Since (−)-pinanediol is known to direct stereoselectively the formation of (*R*)-α-chloroboronic esters,[8,13] the *R* absolute configuration could be assigned to 1-chloropropaneboronate **5**. Most conveniently, isolation and purification of chloro derivative **5** could be avoided, and the subsequent nucleophilic displacement with (benzyloxy)lithium at −78 °C in THF[5] was actually carried out via a one-pot homologation–substitution sequence, which afforded 1-benzyloxy derivative **6** in 44% overall yield from **4** (Scheme 3). The presence of a small quantity of unreacted **4** did not have any detrimental effect during the reaction on crude α-chloroboronic ester **5**. Boronate **6** features a benzyl-protected hydroxy function with *S* absolute configuration,[20] which corresponds to the desired 5*R* stereochemistry in the target metabolite.[2]

The synthetic route continued with the sequential insertion of the second stereocentre, which was installed again by means of Matteson's asymmetric homologation. Exposure of boronic ester **6** to (dichloromethyl)lithium at −100 °C in THF,[19] followed by zinc chloride (1 M in Et_2O),[8] resulted in the formation of 2-benzyloxy-1-chlorobutaneboronate **7** in 52% yield (Scheme 3). Despite the use of zinc chloride, which is usually employed to improve yield[5,13] and diastereoselectivity,[13] the homologation displayed only incomplete conversion (70% by NMR), although the diastereoselectivity was excellent (d.e. ≥98%).

Completion of the desired C_7 framework of the acidic fragment was achieved by treating compound **7** with vinylmagnesium bromide in THF at −78 °C, to afford 1-vinylbutaneboronate **8** in 33% yield (Scheme 3). Yet again, the homologation–substitution sequence gave higher yields when performed on boronic ester **6** as a one-pot procedure (32% total yield over two steps), which avoided purification of the α-chloro intermediate **7**. Likewise, unreacted **6** did not affect the outcome of the nucleophilic displacement with the vinyl Grignard reagent, but care had to be taken to remove all zinc salts during homologation workup before moving to the substitution reaction. Diastereoisomerically pure alkene **8** already bears the two contiguous stereocentres with the correct final *R*,*R* absolute configuration required by (−)-microcarpalide.

Having successfully played its role as chiral director, the boronic scaffold was removed by exposure to alkaline hydrogen peroxide in THF,[8,13,21] which revealed the masked hydroxy function thus providing alcohol **9** in 89% yield (Scheme 3). Since the reaction is well known to occur with retention of configuration, the same *R*,*R* stereochemistry could be also assigned to allylic alcohol **9**.

Protection of the released hydroxy group in **9** as a benzyl ether was deemed the most convenient one, since the same protecting group was already in place and therefore both could be removed together later in the synthetic sequence. Furthermore, no apparent functional group incompatibility with the subsequent key RCM was to be feared, since successful formation of a closely related 10-membered lactone had been reported in the presence of benzyloxy substituents both at the α and β positions to one of the metathesizing olefinic side chains.[4] Careful treatment of 5-hydroxyhept-6-enoic ester **9** with a stoichometric amount of sodium hydride in DMF at −35 °C in the presence of benzyl bromide provided the desired ether **10** in 48% yield (Scheme 3), along with the free acid **11** (Scheme 4) and the undesired benzyl ester in 16 and 7% yield, respectively. When NaH was used in slight excess (1.3 equiv) at rt instead,[22] the product yield dropped to 2%, and formation of unidentified by-products occurred. The *tert*-butyl protection



Scheme 4. (a) TFA, CH_2Cl_2, rt (100%); (b) DCC, DMAP, CH_2Cl_2, rt (66%); (c) Grubbs' catalyst, CH_2Cl_2, reflux (61%; 43% conversion); (d) $TiCl_4$, CH_2Cl_2, 0 °C (58%).

at the carboxylic group clearly revealed limitations and it is tempting to speculate that the moderate yields observed in the course of the two homologation-substitution sequences might be explained by the occurrence of such a deprotection in stronger basic environments, despite the very low temperature.

Treatment of dibenzyloxy ester **10** with TFA at rt proceeded without incident to afford the desired free acid **11** in quantitative yield (Scheme 4).

2.3. Completion of the total synthesis

Having accomplished the stereoselective synthesis of the required C_7 acid **11**, the stage was set to assemble the diene ester for the key RCM macrocyclization. The appropriate alcohol partner **12** had been already synthesized in our own group through an enantioselective approach.[5] Therefore, acid **11** was coupled to alcohol **12** in the presence of DCC and DMAP in methylene chloride at rt, to provide ester **13** in 66% yield (Scheme 4).

Exposure of diene ester **13** to Grubbs' catalyst (22.5 mol%) under high dilution (0.52 mM) in anhydrous degassed dichloromethane under reflux[9] afforded the expected macrolactone **14** in 61% yield (Scheme 4), though, regrettably, with poor conversion (43%), which could not be improved by increasing the reaction time up to 140 h. Much to our delight, however, the RCM macrocyclization resulted in exclusive formation of (*E*)-oxecin-2-one **14** bearing the desired *trans* geometry at the newly formed double bond (Scheme 4), and no *cis* analogue could be detected. The doublet of doublet at 5.69 ppm in the ^{1}H NMR spectrum displaying a coupling constant $J_{H\text{-}7,H\text{-}8}=15.7$ Hz allowed us to assign the *E* stereochemistry to **14** beyond any shadow of doubt.

Excellent stereoselectivity in the formation of the required *trans* macrolactone by means of RCM has been reported in the course of the recent total synthesis of (−)-microcarpalide by Gurjar et al., using a diene ester nearly identical to **13**, except for the methoxyethoxymethyl (MEM) protecting group at 1′–OH.[4] When compared to their 67% yield, however, our poor conversion, even over a longer reaction time, is puzzling. Admittedly, in fact, such a discrepancy within so closely related metathesizing substrates is difficult to explain, especially in the absence of any inherent functional incompatibility to RCM. In contrast, metathetic ring closure of similar dienes bearing an acetonide group spanning O-5 and O-6 was reported to proceed uneventfully in excellent yield and comparable selectivity, regardless of the hydroxyl protection at C-1′ as MOM[3] or benzyl ether.[5] In those cases, however, the conformational constraint intrinsic to the acetonide protection might have favoured alignment of the two alkene appendages in a cyclisation-friendly conformation, as suggested by Fürstner et al. on similar systems leading to nonenolides.[23] However, such a predisposition toward metathetic ring closure can be also attained by means of acyclic constraints.[9a,e] For instance, the nature of protecting groups at neighbouring allylic and homoallylic hydroxy functions was found to be decisive for the successful formation of 10-membered carbocycles by RCM.[24] Similarly, fine tuning of the protection at the allylic position was required to construct the framework of herbarumin III, a fungal nonenolide, by ring-closing metathesis, either with Grubbs' first or second generation catalyst.[25]

Although it cannot be excluded a priori that even a remote appendage might exert a dramatic effect in the formation of 10-membered macrocycles by RCM, this hypothesis remains undoubtedly a topic for further investigations which will have to be verified over a broader range of substrates. In this respect, the influence of remote substituents on the *E*/*Z* ratio in ring-closing metathesis has been reported for larger ring systems, such as epothilones[26] and salicylihalamides,[27] which feature a 16- and 12-membered lactone skeleton, respectively. Yet again, the strong dependency of the metathetic process on the intimate nature of the 1,ω-diene substrate itself, and especially of its appendages, *either close or remote*, is posing considerable challenges at drawing up general and reliable guidelines for controlling the formation of medium-sized rings by RCM, even within a given ring size and catalyst.

Completion of the total synthesis required cleavage of the three benzyl groups protecting the hydroxy functions at positions 5, 6 and 1′. Accordingly, tribenzyl ether **14** was treated with $TiCl_4$ in dichloromethane at 0 °C[5] to afford the target metabolite (**1**) in 58% yield (Scheme 4). The product had spectral properties in perfect agreement with those

reported in the literature for synthetic[5] and natural microcarpalide (**1**).[2]

3. Conclusions and future prospects

To date, five different syntheses of microcarpalide are available in the literature,[3–7] although, for the sake of stereochemical accuracy, four of them only have dealt with the natural (−) enantiomer.[3–5,7] In all cases except one,[7] at least one of the two key subunits was prepared from the chiral pool.[3–6] Ishigami and Kitahara, in constrast, employed an original convergent approach that featured two different Sharpless asymmetric dihydroxylations to install the four stereocentres, and a Julia olefination followed by Yamaguchi macrolactonization for the final assembly of the oxecin-2-one scaffold.[7]

In the present case, all four stereocentres have been installed by asymmetric synthesis using (+)- or (−)-pinanediol as chiral auxiliary during stereoselective homologations of appropriate boronic esters. Final steps included DCC-mediated coupling of the two chiral synthons (**11** and **12**) bearing appropriate terminal alkene appendages, stereoselective ring-closing metathesis of the resulting diene ester (**13**) and ultimate release of the three protected hydroxy functions by treatment with titanium tetrachloride.

The enantioselective route herein disclosed represents a flexible and convergent approach to microcarpalide and analogues thereof, which should be of value in the framework of SAR studies aiming at shedding light on the mechanism of action of this peculiar fungal metabolite, whose original endophytic producer has meanwhile been lost.[28] Moreover, the stepwise insertion of stereocenters by means of Matteson's asymmetric homologation would also allow the introduction of suitably labelled atoms at defined positions, a feature that could be appealing for future biological studies.

Microcarpalide (**1**) bears structural resemblance to a family of phytotoxins such as herbarumins[29] and pinolidoxin,[30] with which it shares a common nonenolide architecture. These fungal toxins interfere with the self-defense system in plants and might, therefore, hold promise as lead compounds for developing new herbicidal agents.[23,31] Although the phytotoxicity of microcarpalide has not been tested as yet, it is tempting to suggest that a similar biological activity might also occur.

Furthermore, a number of 10-membered lactones of polyketide biosynthetic origin are currently being isolated from a variety of fungal species,[32] endophytic fungi included,[33] and it is likely that these organisms might well harbour a much greater chemical diversity in this respect. Most interestingly, these fungal nonenolides are endowed with the most diverse biological activities, and might, therefore, represent a promising class of future lead structures for a variety of applications. Yet again, design and synthesis of analogues should be of great value to gain some insight into structure-activity relationships within this fascinating family of fungal metabolites.

4. Experimental

4.1. General

All solvents used were anhydrous, unless stated otherwise, and all reactions requiring anhydrous conditions were performed using oven-dried and argon-flushed glassware. Anhydrous tetrahydrofuran and diethyl ether were prepared by standard methods and freshly distilled over sodium benzophenone ketyl prior to use. Dichloromethane and *N*,*N*-dimethylformamide were dried according to standard procedures and stored upon 3 Å molecular sieves. Acetone was dried over potassium carbonate. (1*R*,2*R*,3*S*,5*R*)-(−)-Pinanediol, dibromomethane, *tert*-butylacetate and all other reagents were obtained from Aldrich. (−)-Pinanediol chloromethaneboronate (**3a**) was prepared following the procedure described by Strynadka and colleagues,[15] except for the replacement of chloroiodomethane with bromochloromethane (**2a**) as the starting material. First generation Grubbs' catalyst [bis(tricyclohexylphosphine) benzylidine ruthenium(IV) dichloride] was purchased from Strem Ltd and maintained in a Schlenk flask under Ar atmosphere. Chromatographic purification of compounds was carried out on silica gel (60–200 μm). Details of analytical TLC have been already described.[5]

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution (except for **1**, for which CD_3CN was used)[2,5] on a Bruker DPX200 or Avance 400 spectrometer; chemical shifts (δ) are reported in ppm downfield from TMS as internal standard (s singlet, d doublet, t triplet, q quartet, m multiplet, br broad signal); coupling constants (J) are given in Hz Two-dimensional NMR techniques (COSY, HMBC, HSQC) were utilized to aid in the assignment of signals in ^{1}H and ^{13}C spectra, in particular for 5,6,1′-*O*,*O*,*O*-tribenzylmicrocarpalide (**14**). IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer; wavenumbers (ν_{max}) are in cm^{-1}. For mass spectra determinations a Finnigan MAT SSQ A and a Hewlett-Packard HP5972 spectrometer were used (EI, 70 eV). Elemental analyses were performed with a Carlo Erba Elemental Analyzer mod. 1110. Optical rotations were measured in chloroform at 20 °C with a Perkin–Elmer 241 polarimeter and are expressed in 10^{-1} deg cm^2 g^{-1}; concentration (c) is in g 100 mL^{-1}.

4.1.1. (−)-Pinanediol bromomethaneboronate (3b). Commercially available dibromomethane (2.03 mL, 29.08 mmol) and freshly distilled trimethyl borate (2.81 mL, 25.10 mmol) were dissolved in THF (20 mL) in a 4-necked 100-mL flask equipped with two dropping funnels and a mechanical stirrer, and cooled to −78 °C. *n*-Butyllithium (2.5 M solution in hexanes, 10.5 mL, 26.25 mmol) was slowly added dropwise under Ar flow over a 40 min period, using additional THF (5 mL) for washing. After stirring for 1 h, bromotrimethylsilane (3.84 mL, 29.09 mmol) was introduced, washing with THF (5 mL). Formation of a white precipitate occurred. The suspension was left to warm to rt overnight, and an orange–yellow clear solution was obtained. A solution of (1*R*,2*R*,3*S*,5*R*)-(−)-pinanediol (4.5 g, 26.43 mmol) in dry THF (17 mL) was then added at rt under Ar flow and left to react for 1 h. The reaction mixture was partitioned between

ethyl acetate (230 mL) and water (50 mL) and phases were separated. The aqueous layer was extracted with ethyl acetate (3×30 mL) and the pooled organic phases were dried (Na_2SO_4). After filtration and concentration in vacuo, the crude liquid was purified by chromatography with light petroleum/ethyl acetate 70:30, affording bromomethaneboronate **3b** as a pale yellow oil (5.017 g, 73% yield), $[\alpha]_D=-22.5$ (*c* 2.8, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.80 (3H, s, pinanyl CH_3), 1.16 (1H, d, $J=11.0$ Hz, pinanyl H_{endo}), 1.25 (3H, s, pinanyl CH_3), 1.37 (3H, s, pinanyl CH_3), 1.71–2.39 (5H, m, pinanyl protons), 2.57 (2H, s, CH_2Br), 4.32 (1H, dd, $J=8.7$, 1.8 Hz, C*H*OB). ^{13}C NMR: δ 8.2 (br, *C*B), 23.9, 26.2, 27.0, 28.4, 35.2, 38.2, 39.3, 51.2, 78.5, 86.7. IR (neat): ν_{max} 1242, 1340, 1416. MS, *m*/*z*: 272–274 (1:1, M^+, 11), 257–259 (1:1, 32), 231 (33), 216–218 (1:1, 30), 203–205 (1:1, 52), 189 (25), 176 (26), 152 (25), 134 (74), 119 (30), 109 (30), 96 (80), 83 (100), 81 (66), 67 (62), 55 (51%). Anal. Calcd for $C_{11}H_{18}BBrO_2$: C, 48.40; H, 6.65. Found: C, 48.48; H, 6.71.

4.1.2. (−)-Pinanediol iodomethaneboronate (3c). A solution of (−)-pinanediol chloromethaneboronate (**3a**)[15] (1.01 g, 4.42 mmol) in dry acetone (7 mL) was added dropwise at rt over 5 min to a stirred solution of sodium iodide in acetone (14 mL). The flask was wrapped in aluminium foil to protect from light. Formation of a white powdery precipitate was observed. After 3 h, the dark yellow suspension was repeatedly centrifuged and the clear solution was pipetted off, washing the residual solid with diethyl ether. The pooled organic phases were evaporated to dryness, partitioned between satd $Na_2S_2O_5$ (15 mL) and diethyl ether (50 mL), and the organic layer was washed with brine (10 mL) and water (10 mL). After drying over Na_2SO_4 and filtration, the solvent was evaporated under reduced pressure to afford iodo derivative **3c** (1.223 g, 86% yield) as a dense yellow liquid which turned brown upon prolonged exposure to light. $[\alpha]_D=-23.6$ (*c* 3.2, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.88 (3H, s, pinanyl CH_3), 1.28 (1H, d, $J=10.5$ Hz, pinanyl H_{endo}), 1.33 (3H, s, pinanyl CH_3), 1.43 (3H, s, pinanyl CH_3), 1.85−2.00 (2H, m, pinanyl protons), 2.12 (1H, t, $J=5.1$ Hz, pinanyl proton), 2.24 (2H, s, CH_2I), 2.25–2.56 (2H, m, pinanyl protons), 4.40 (1H, dd, $J=8.8$, 2.0 Hz, C*H*OB). ^{13}C NMR: δ −22.8 (br, I*C*B), 25.3, 27.7, 28.4, 29.7, 36.7, 39.8, 40.7, 52.8, 79.9, 87.9. IR (neat): ν_{max} 1241, 1380. MS, *m*/*z*: 320 (M^+, 66), 305 (64), 291 (5), 277 (30), 265 (58), 251 (98), 224 (92), 193 (3), 179 (14), 152 (33), 134 (79), 127 (19), 124 (43), 96 (52), 83 (100), 67 (89), 55 (73%). Anal. Calcd for $C_{11}H_{18}BIO_2$: C, 41.29; H, 5.67. Found: C, 41.33; H, 5.51.

4.1.3. (−)-Pinanediol 2-[*tert*-butoxycarbonyl]ethaneboronate (4). In a four-necked 100-mL flask, (−)-pinanediol bromomethaneboronate (**3b**) (5.017 g, 18.38 mmol) and *tert*-butyl acetate (2.97 mL, 22.06 mmol) were dissolved in freshly distilled THF (23 mL) and cooled to −78 °C. In a separate flask, fresh LDA was prepared by treating diisopropylamine (3.09 mL, 22.06 mmol) with *n*-butyllithium (2.5 M solution in hexanes, 8.1 mL, 20.22 mmol) in THF (11 mL) at −78 °C, followed by gradual warming to rt over 1 h. The LDA solution thus formed was slowly added via syringe at −78 °C under magnetic stirring and Ar flow over a 30 min period. After leaving to warm to rt overnight, the reaction mixture was partitioned between light petroleum (100 mL) and satd NH_4Cl (180 mL). The aqueous layer was extracted with light petroleum (2×85 mL) and the combined organic phases were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a syrupy orange liquid. After chromatographic purification using light petroleum/diethyl ether 80:20 as the eluant, the title compound **4** (4.254 g, 75% yield) was obtained as a dense pale yellow oil, $[\alpha]_D=-17.5$ (*c* 1.0, $CHCl_3$). Following the same procedure, the title compound could be also prepared from halomethaneboronates **3a** and **3c**, albeit in lower yield (28% and 65%, respectively). When **3a** was used, *tert*-butylacetoacetate was also recovered[11] after column chromatography in addition to the unreacted substrate. ^{1}H NMR (200 MHz): δ 0.72 (3H, s, pinanyl CH_3), 1.03 (2H, t, $J=7.5$ Hz, *H*-1), 1.19 (1H, d, $J=10.8$ Hz, pinanyl H_{endo}), 1.29 (3H, s, pinanyl CH_3), 1.37 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.70–2.30 (5H, m, pinanyl protons), 2.36 (2H, t, $J=7.5$ Hz, *H*-2), 4.27 (1H, dd, $J=8.7$, 2.0 Hz, pinanyl C*H*OB). ^{13}C NMR: δ 6.8 (br, *C*B), 25.3, 27.7, 28.5, 29.5, 29.9, 31.4, 36.8, 39.5, 40.9, 52.7, 79.2, 81.1, 86.9, 175.0. IR (neat): ν_{max} 1150, 1390, 1731. MS, *m*/*z*: 252 ($[M-56]^+$, 2), 235 (1), 210 (0.4), 196 (0.7), 181 (27), 167 (10), 154 (22), 135 (50), 119 (13), 109 (25), 99 (46), 93 (49), 83 (41), 67 (28), 57 (100), 55 (41), 43 (26%). Anal. Calcd for $C_{17}H_{29}BO_4$: C, 66.25; H, 9.48. Found: C, 66.31; H, 9.40.

4.1.4. (−)-Pinanediol (1*R*)-3-[*tert*-butoxycarbonyl]-1-chloropropaneboronate (5). A solution of methylene chloride (260 μL, 4.06 mmol) in THF (5 mL) was cooled at −100 °C and treated with a 2.5 M solution of *n*-butyllithium in hexanes (930 μL, 2.32 mmol) under Ar flow and mechanical stirring. After 55 min, the solution of boronate **4** (618 mg, 2.02 mmol) in THF (6 mL) was added dropwise at −100 °C over a 20 min period and the flask was warmed to −78 °C. Zinc chloride (1 M solution in diethyl ether, 3.6 mL, 3.64 mmol) was then added during a 20 min period, washing with THF (2 mL), and the reaction mixture was left to stir at rt for 22 h. After dilution with light petroleum (70 mL), the mixture was washed repeatedly with water (5×35 mL) and concentrated in vacuo. The residue was dissolved again in light petroleum (50 mL) and washed with water (2×25 mL) for complete removal of zinc salts. The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. Chromatographic purification of the crude residue with light petroleum/ethyl acetate 80:20 afforded the desired product **5** in 90% purity (by NMR) as a dense pale yellow oil (520 mg, 66% yield), $[\alpha]_D=-26.1$ (*c* 4.6), whilst unreacted substrate **4** accounted for the remainder 10%. ^{1}H NMR (200 MHz): δ 0.84 (3H, s, pinanyl CH_3), 1.17 (1H, d, $J=10.9$ Hz, pinanyl H_{endo}), 1.29 (3H, s, pinanyl CH_3), 1.42 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.84–2.58 (9H, m, 5 pinanyl protons, 2×*H*-2, 2×*H*-3), 3.51 (1H, dd, $J=9.0$, 5.4 Hz, *H*-1), 4.36 (1H, dd, $J=8.7$, 1.8 Hz, pinanyl C*H*OB). ^{13}C NMR: δ 25.2, 27.6, 28.3, 29.4, 29.7, 30.6, 34.2, 36.5, 39.5, 40.7, 43.7 (br, Cl*C*HB), 52.5, 79.8, 81.5, 87.9, 173.3. MS, *m*/*z*: 300–302 (3:1, $[M-56]^+$, 2), 285–287 (3:1, 1), 256–258 (3:1, 0.5), 249 (0.5), 231–233 (3:1, 26), 215 (2), 204 (10), 179 (4), 161 (11), 149 (11), 135 (69), 109 (22), 99 (64), 93 (45), 83 (31), 67 (30), 57 (100), 55 (39), 44 (6%).

4.1.5. (−)-Pinanediol (1*S*)-1-benzyloxy-3-[*tert*-butoxycarbonyl]propaneboronate (6). A solution of boronate **4** (2.11 g, 6.85 mmol) in THF (7 mL) was slowly added at −100 °C over 15 min to a mechanically stirred solution of (dichloromethyl)lithium prepared from CH_2Cl_2 (882 μL, 13.76 mmol) and *n*-BuLi (2.5 M solution in hexanes, 3.2 mL, 8 mmol) in THF (8 mL) at −100 °C, by close analogy to the procedure reported above. Subsequently, a 1 M solution of $ZnCl_2$ in diethyl ether (12.3 mL, 12.3 mmol) was added at −78 °C over a 20 min period, washing with THF (3 mL), and the mixture was left to stir at rt. After 18 h the reaction mixture was diluted with light petroleum (70 mL), washed with water (4×35 mL), evaporated to dryness, dissolved in fresh light petroleum (50 mL) and re-washed with water (4×25 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuo to yield chloro boronate **5** as a yellow liquid (2.24 g) which was used without further purification. In a separate 50-mL flask equipped with a reflux condenser, benzyl alcohol (671 μL, 6.48 mmol) was dissolved in THF (3 mL) and titrated with a 2.5 M solution of *n*-BuLi in hexanes (2.8 mL, 7.0 mmol) at −78 °C under magnetic stirring and Ar flow in the presence of a few crystals of oven-dried (110 °C, 2 h) 1,10-phenanthroline as indicator, until the colour turned dark red. The mixture was then stirred at −78 °C for 15 min and briefly warmed to rt for 5 min. Subsequently, a solution of crude **5** (2.24 g) in THF (7 mL) was slowly dropped in at −78 °C, whereupon the solution turned lemon yellow in colour. After leaving to warm to rt overnight, the reaction mixture was heated under reflux for 2 h under Ar atmosphere until TLC showed disappearance of the homologation product **5**. The mixture was then partitioned between light petroleum (45 mL) and satd NH_4Cl (45 mL), phases were separated and the aqueous layer was extracted with diethyl ether (3×35 mL). The combined organic phases were dried (Na_2SO_4), filtered and evaporated under reduced pressure to give a viscous dark yellow oil. Chromatographic purification with light petroleum/diethyl ether 90:10 as the eluant afforded the title compound **6** as a dense bright yellow oil (1.304 g, 44% yield over two steps), $[\alpha]_D=-0.79$ (*c* 1.2, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.84 (3H, s, pinanyl CH_3), 1.15 (1H, d, $J=10.7$ Hz, pinanyl H_{endo}), 1.30 (3H, s, pinanyl CH_3), 1.40 (3H, s, pinanyl CH_3), 1.43 (9H, s, *t*-Bu), 1.84–2.38 (7H, m, 5 pinanyl protons and 2×*H*-2), 2.39 (2H, t, $J=7.7$ Hz, *H*-3), 3.36 (1H, dd, $J=7.3$, 5.9 Hz, *H*-1), 4.32 (1H, dd, $J=8.6$, 1.8 Hz, pinanyl C*H*OB), 4.50 (1H, d, $J=11.9$ Hz, CH_2Ph), 4.61 (1H, d, $J=11.9$ Hz, CH_2Ph), 7.20–7.39 (5H, m, arom). ^{13}C NMR: δ 25.3, 27.9, 28.1, 28.4, 29.5, 30.0, 33.9, 36.7, 39.5, 40.9, 52.6, 67.9 (br, *C*HB), 73.6, 79.5, 81.3, 87.6, 128.7, 129.2, 129.6, 140.3, 174.4. IR (neat): ν_{max} 698, 736, 1150, 1374, 1730. MS, *m/z*: 429 ($[M+1]^+$, 2), 373 (3), 355 (9), 281 (11), 265 (7), 225 (2), 179 (2), 153 (27), 135 (59), 109 (13), 93 (25), 91 (100), 57 (27%). Anal. Calcd for $C_{25}H_{37}BO_5$: C, 70.10; H, 8.71. Found: C, 70.33; H, 8.55.

4.1.6. (−)-Pinanediol (1*R*,2*R*)-2-benzyloxy-4-[*tert*-butoxycarbonyl]-1-chlorobutaneboronate (7). By close analogy to the synthesis of **5**, (dichloromethyl)lithium was prepared by treatment of dichloromethane (195 μL, 3.04 mmol) in THF (6 mL) with *n*-BuLi (2.5 M solution in hexanes, 0.7 mL, 1.75 mmol) at −100 °C. Benzyl ether **6** (648 mg, 1.51 mmol) was dissolved in THF (6 mL) and added dropwise over 20 min to the (dichloromethyl)lithium solution at −100 °C, under mechanical stirring and Ar flow. The reaction mixture was then warmed to −78 °C and $ZnCl_2$ (1 M solution in Et_2O, 1.66 mL, 1.66 mmol) was introduced. After leaving to warm to rt overnight, the mixture was diluted with light petroleum (200 mL) washed with water (4×100 mL), evaporated to dryness, dissolved again in fresh light petroleum (130 mL) and thoroughly washed with water (4×80 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford a dense dark yellow oil (532 mg, 52% yield), $[\alpha]_D=-5.6$ (*c* 2.1), which was used as such for the next step. In addition to the desired homologation product (**7**), NMR analysis revealed also the presence of 30% of unreacted substrate. ^{1}H NMR (200 MHz): δ 0.85 (3H, s, pinanyl CH_3), 1.22 (1H, d, $J=10.8$ Hz, pinanyl H_{endo}), 1.30 (3H, s, pinanyl CH_3), 1.41 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.84–2.43 (7H, m, 5 pinanyl protons and 2×*H*-3), 2.35 (2H, t, $J=7.4$ Hz, *H*-4), 3.63 (1H, d, $J=6.6$ Hz, *H*-1), 3.83 (1H, ddd, $J=7.4$, 6.6, 4.7 Hz, *H*-2), 4.38 (1H, dd, $J=8.6$, 2.0 Hz, pinanyl C*H*OB), 4.60 (1H, d, $J=11.2$ Hz, CH_2Ph), 4.72 (1H, d, $J=11.2$ Hz, CH_2Ph), 7.25–7.40 (5H, m, arom). ^{13}C NMR: δ 25.3, 27.7, 28.4, 28.9, 29.5, 29.8, 32.8, 36.6, 39.6, 40.7, 46.2 (br, Cl*C*HB), 52.6, 74.1, 80.0, 80.9, 81.6, 88.3, 129.0, 129.2, 129.7, 139.7, 173.9. The EI-MS was unobtainable.

4.1.7. (−)-Pinanediol (1*R*,2*R*)-2-benzyloxy-4-[*tert*-butoxycarbonyl]-1-vinylbutaneboronate (8). Following the same procedure reported above, (dichloromethyl)-lithium was prepared by treating methylene chloride (396 μL, 6.17 mmol) in THF (4 mL) with *n*-BuLi (2.5 M solution in hexanes, 1.43 mL, 3.58 mmol) at −100 °C. A solution of benzyloxy derivative **6** (1.317 g, 3.07 mmol) in THF (7 mL) was added dropwise at −100 °C over a 15 min period, and the temperature was raised to −78 °C. Zinc chloride (1 M solution in Et_2O, 5.5 mL, 5.5 mmol) was introduced and the reaction mixture was left to warm to rt overnight. Similarly as above, the mixture was diluted with light petroleum (200 mL) washed with water (4×100 mL), concentrated in vacuo, dissolved in fresh light petroleum (70 mL) and washed again with water (4×50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give crude α-chloro derivative **7** as a dense bright yellow oil (1.256 g) which was employed immediately for the substitution reaction without further purification. Vinylmagnesium bromide (1 M solution in THF, 3.2 mL, 3.2 mmol) was added dropwise via syringe over 10 min to a stirred solution of crude **7** in THF (20 mL) at −78 °C and the mixture was left to react for 1 h at this temperature. After warming to rt overnight, the reaction mixture was partitioned between light petroleum (90 mL) and satd ammonium chloride (60 mL). Phases were separated and the aqueous layer was extracted with light petroleum (3×30 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark yellow residue. Purification by column chromatography using light petroleum/diethyl ether mixtures of increasing polarity (from 100 to 80:20) as eluants, afforded vinyl derivative **8** as a bright yellow dense liquid (459 mg) in 32% overall yield (over two steps), $[\alpha]_D=+3.8$ (*c* 1.6, $CHCl_3$). ^{1}H NMR (200 MHz): δ 0.82 (3H, s, pinanyl CH_3), 1.13 (1H, d, $J=10.2$ Hz, pinanyl

H_{endo}), 1.26 (3H, s, pinanyl CH_3), 1.33 (3H, s, pinanyl CH_3), 1.44 (9H, s, *t*-Bu), 1.74–2.42 (10H, m, 5 pinanyl protons, *H*-1, 2×*H*-3 and 2×*H*-4), 3.74 (1H, ddd, J=7.7, 6.6, 4.1 Hz, *H*-2), 4.26 (1H, dd, J=8.7, 2.0 Hz, pinanyl C*H*OB), 4.52 (1H, d, J=11.5 Hz, CH_2Ph), 4.59 (1H, d, J=11.5 Hz, CH_2Ph), 5.04 (1H, dd, J=9.9, 2.0 Hz, CH=CH_2), 5.10 (1H, ddd, J=17.1, 2.0, 0.8 Hz, CH=CH_2), 5.84 (1H, dt, J=17.1, 9.9 Hz, C*H*=CH$_2$), 7.20–7.36 (5H, m, arom). ^{13}C NMR: δ 25.3, 27.6, 28.4, 29.0, 29.5, 29.9, 32.2, 36.7, 39.5, 40.8, 52.7, 72.4, 79.2, 80.7, 81.3, 87.1, 117.4, 128.6, 129.0, 129.5, 137.0, 140.2, 174.5 (*C*HB not seen). IR (neat): ν_{max} 697, 736, 905, 992, 1152, 1636, 1730. MS, *m*/*z*: 469 ([M+1]$^+$, 0.4), 413 (0.3), 397 (0.7), 305 (1), 249 (5), 217 (2), 193 (54), 159 (12), 135 (18), 106 (26), 91 (100), 79 (10), 57 (16%). Anal. Calcd for $C_{28}H_{41}BO_5$: C, 71.79; H, 8.82. Found: C, 71.65; H, 9.01.

4.1.8. (4*R*,5*R*)-4-Benzyloxy-5-hydroxyhept-6-enoic acid *tert*-butyl ester (9). Vinyl boronate **8** (537 mg, 1.15 mmol) was dissolved in THF (10 mL) and treated with sodium hydroxide (2.2 M solution, 1.56 mL, 3.44 mmol) at 0 °C for 10 min under magnetic stirring. Upon addition of hydrogen peroxide (35% w/w solution, 272 μL, 3.11 mmol) at 0 °C, a white precipitate formed. After 15 min at 0 °C, the cloudy solution was stirred at 45 °C for an additional 1 h until TLC analysis (light petroleum/diethyl ether 50:50) revealed disappearance of the starting boronate. The reaction mixture was partitioned between diethyl ether (40 mL) and water (20 mL), phases were separated and the aqueous layer was extracted with diethyl ether (3×10 mL). The pooled organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. Purification of the thick yellow residue by column chromatography, using light petroleum/diethyl ether 70:30 as the eluant, afforded the title compound **9** (313 mg, 89% yield) as a dense pale yellow oil, $[\alpha]_D$=+14.0 (*c* 1.6, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.45 (9H, s, *t*-Bu), 1.73–2.06 (2H, m, *H*-3), 2.20–2.48 (1H, br, CHO*H*), 2.36 (2H, t, J=7.5 Hz, *H*-2), 3.44 (1H, m, *H*-4), 4.09 (1H, tt, J=5.9, 1.4 Hz, *H*-5), 4.58 (1H, d, J=11.3 Hz, CH_2Ph), 4.66 (1H, d, J=11.3 Hz, CH_2Ph), 5.24 (1H, dt, J=10.5, 1.4 Hz, *H*-7), 5.38 (1H, dt, J=17.2, 1.4 Hz, *H*-7), 5.91 (1H, ddd, J=17.2, 10.5, 5.9 Hz, *H*-6), 7.25–7.45 (5H, m, arom). ^{13}C NMR: δ 25.8, 28.1, 31.0, 72.9, 74.3, 80.3, 81.1, 116.9, 127.8, 127.9, 128.5, 137.4, 138.1, 172.8. IR (neat): ν_{max} 698, 736, 923, 994, 1094, 1154, 1455, 1497, 1729, 3454 (br). MS, *m*/*z*: 306 (M$^+$, 0.5), 305 (1), 265 (1), 249 (0.3), 232 (0.4), 214 (1), 193 (44), 173 (1), 155 (1), 129 (26), 91 (100), 73 (24), 57 (9), 41 (5%). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.75; H, 8.48.

4.1.9. (4*R*,5*R*)-4,5-Dibenzyloxyhept-6-enoic acid *tert*-butyl ester (10). Sodium hydride (60% suspension in mineral oil, 22 mg, 0.55 mmol) was slurried in DMF (1.1 mL) and added via syringe to a stirred solution of alcohol **9** (162 mg, 0.53 mmol) and benzyl bromide (69 μL, 0.58 mmol) in DMF (0.8 mL) at −35 °C. Vigorous gas release was observed. The reaction mixture was stirred at −35 °C for 1 h 10 min, warmed to −20 °C during 1 h and finally kept at −10 °C for an additional 1 h. After quenching with cold water (10 mL), the mixture was extracted with light petroleum (4×15 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. Filtration and rotary evaporation afforded a dark yellow crude residue which was purified by chromatography on silica gel, eluting with light petroleum/diethyl ether mixtures from 100 to 50:50. The desired dibenzyl ether **10** was obtained (93 mg, 44% yield) as a dense pale yellow oil, along with (4*R*,5*R*)-4,5-dibenzyloxy-hept-6-enoic acid (**11**, 29 mg), (4*R*,5*R*)-4,5-dibenzyloxy-hept-6-enoic acid benzyl ester (16 mg) and unreacted **9** (13 mg). The undesired benzyl ester was identified on the basis of ^{1}H NMR spectroscopy only (data not shown).

Compound **10**: $[\alpha]_D$=+9.5 (*c* 1.7, $CHCl_3$). ^{1}H NMR (200 MHz): δ 1.45 (9H, s, *t*-Bu), 1.62–2.02 (2H, m, *H*-3), 2.20–2.46 (2H, m, *H*-2), 3.55 (1H, ddd, J=9.2, 5.9, 3.7 Hz, *H*-4), 3.92 (1H, dd, J=7.4, 5.9 Hz, *H*-5), 4.43 (1H, d, J=12.0 Hz, CH_2Ph), 4.57 (1H, d, J=11.4 Hz, CH_2Ph), 4.66 (1H, d, J=12.0 Hz, CH_2Ph), 4.78 (1H, d, J=11.4 Hz, CH_2Ph), 5.28–5.38 (2H, m, *H*-7), 5.86 (1H, ddd, J=16.2, 11.4, 7.4 Hz, *H*-6), 7.25–7.44 (10H, m, arom). ^{13}C NMR: δ 26.3, 28.1, 31.6, 70.6, 73.4, 80.0, 80.2, 82.7, 118.9, 127.45, 127.53, 127.7, 128.0, 128.3, 135.1, 138.5, 138.7, 172.9. IR (neat): ν_{max} 697, 734, 929, 997, 1072, 1165, 1455, 1497, 1734. MS, *m*/*z*: 339 ([M−57]$^+$, 0.2), 249 (2), 232 (0.6), 193 (29), 181 (5), 143 (2), 125 (3), 101 (2), 92 (6), 91 (100), 85 (2), 65 (4), 57 (5%). Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.94; H, 7.98.

4.1.10. (4*R*,5*R*)-4,5-Dibenzyloxyhept-6-enoic acid (11). *tert*-Butyl ester **10** (93 mg, 0.23 mmol) was dissolved in dichloromethane (1 mL) and stirred at rt in the presence of TFA (520 μL, 7.0 mmol), until disappearance on TLC (light petroleum/diethyl ether 80:20) occurred. After 2 h the reaction mixture was evaporated under reduced pressure to afford the free acid **11** (80 mg, 100% yield) as a dense light brown oil, $[\alpha]_D$=+9.7 (*c* 1.5, $CHCl_3$), which was used without further purification for the next DCC-mediated coupling reaction. ^{1}H NMR (200 MHz): δ 1.66–2.04 (2H, m, *H*-3), 2.22–2.56 (2H, m, *H*-2), 3.57 (1H, ddd, J=9.2, 5.8, 3.6 Hz, *H*-4), 3.95 (1H, dd, J=7.4, 5.8 Hz, *H*-5), 4.42 (1H, d, J=11.9 Hz, CH_2Ph), 4.56 (1H, d, J=11.4 Hz, CH_2Ph), 4.67 (1H, d, J=11.9 Hz, CH_2Ph), 4.78 (1H, d, J=11.4 Hz, CH_2Ph), 5.29–5.39 (2H, m, *H*-7), 5.84 (1H, ddd, J=16.4, 11.2, 7.4 Hz, *H*-6), 7.19–7.42 (10H, m, arom), 8.10–8.40 (1H, br, COO*H*). ^{13}C NMR: δ 25.9, 30.3, 70.6, 73.4, 79.9, 82.5, 119.2, 127.6, 127.7, 127.8, 128.1, 128.4, 134.9, 138.3, 179.8. IR (neat): ν_{max} 698, 736, 931, 995, 1071, 1454, 1497, 1709, 3064 (br). MS, *m*/*z* (as the corresponding methyl ester, obtained by treatment with diazomethane in diethyl ether): 354 (M$^+$, 0.02), 263 (0.4), 246 (8), 207 (14), 157 (4), 140 (4), 115 (6), 91 (100), 65 (6). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.18; H, 7.02.

4.1.11. (4*R*,5*R*)-4,5-Dibenzyloxyhept-6-enoic acid, (1′*S*,1″*S*)-1′-(1″-benzyloxyheptyl)-3′-butenyl ester (13). (4*S*,5*S*)-5-Benzyloxyundec-1-en-4-ol (**12**)[5] (37 mg, 0.134 mmol) was dissolved in methylene chloride (3.5 mL) and added via syringe to a stirred solution of acid **11** (48 mg, 0.141 mmol) in the same solvent (1 mL). DCC (35 mg, 0.17 mmol) and DMAP (3 mg, 0.025 mmol) were added at rt and the reaction mixture was stirred for 25 h. After removal of the white powdery precipitate, the solvent was evaporated in vacuo and the crude residue was purified by chromatography with light petroleum/diethyl

ether 90:10 to afford ester **13** as a dense pale yellow liquid (53 mg, 66% yield), $[\alpha]_D = +1.9$ (*c* 1.4, $CHCl_3$). ^1H NMR (200 MHz): δ 0.89 (3H, t, $J=6.5$ Hz, *H*-7″), 1.06–2.09 (12H, m, *H*-2″ to *H*-6″, *H*-3), 2.23–2.56 (4H, m, *H*-2 and *H*-2′), 3.41–3.64 (2H, m, *H*-4 and *H*-1″), 3.92 (1H, dd, $J=$ 7.3, 6.0 Hz, *H*-5), 4.42 (1H, d, $J=12.0$ Hz, CH_2Ph), 4.54 (1H, d, $J=11.4$ Hz, CH_2Ph), 4.60 (2H, s, PhCH_2OC-1″), 4.65 (1H, d, $J=12.0$ Hz, CH_2Ph), 4.75 (1H, d, $J=11.4$ Hz, CH_2Ph), 4.95–5.15 (3H, m, *H*-1′ and 2×*H*-4′), 5.25–5.37 (2H, m, *H*-7), 5.62–5.92 (2H, m, *H*-6 and *H*-3′), 7.22–7.43 (15H, m, arom). ^{13}C NMR: δ 14.0, 22.6, 25.6, 26.3, 29.4, 29.9, 30.6, 31.7, 34.3, 70.6, 72.3, 73.2, 73.4, 79.0, 80.2, 82.6, 117.5, 119.0, 127.5, 127.6, 127.7, 127.8, 127.9, 128.3, 134.2, 135.1, 138.5, 138.56, 138.62, 173.1. IR (neat): ν_{max} 734, 911, 930, 997, 1070, 1109, 1454, 1497, 1735, 2856, 2927, 3031, 3055. MS, *m/z*: 599 ($[M+1]^+$, 0.4), 507 (0.5), 491 (0.3), 451 (5), 401 (2), 384 (1), 349 (1), 293 (2), 259 (9), 253 (5), 233 (3), 205 (2), 181 (30), 135 (5), 125 (8), 113 (6), 91 (100), 85 (16), 65 (5%). Anal. Calcd for $C_{39}H_{50}O_5$: C, 78.22; H, 8.42. Found: C, 78.39; H, 8.47.

4.1.12. (5*R*,6*R*,7*E*,10*S*)-10-[(1′*S*)-1′-Benzyloxyheptyl]-5,6-dibenzyloxy-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one (14). First generation Grubbs' catalyst (22 mg, 0.027 mmol) was added to a solution of diene ester **13** (72 mg, 0.12 mmol) in freshly distilled degassed anhydrous dichloromethane (230 mL) and the mixture was heated under reflux under Ar flow. Air was then bubbled in under vigorous magnetic stirring to favour catalyst decomposition and the solvent was evaporated under reduced pressure, affording a dark brown oily residue which was chromatographed using light petroleum/diethyl ether mixtures of increasing polarity (from 100 to 70:30) as eluants to provide the title oxecine **14** (18 mg, 26% yield), $[\alpha]_D = -28.8$ (*c* 1.5, $CHCl_3$), along with unreacted diene **13** (41 mg). ^1H NMR (400 MHz): δ 0.93 (3H, t, $J=6.8$ Hz, *H*-7′), 1.22–1.52 (8H, br m, *H*-3′ to *H*-6′), 1.54–1.70 (2H, m, *H*-2′), 2.01–2.17 (1H, m, *H*-4), 2.17–2.27 (1H, m, *H*-3), 2.27–2.39 (3H, m, *H*-4 and 2×*H*-9), 2.60–2.72 (1H, m, *H*-3), 3.47–3.57 (1H, m, *H*-1′), 3.76 (1H, t, $J=5.4$ Hz, *H*-5), 4.14 (1H, br d, $J=$ 4.9 Hz, *H*-6), 4.52 (1H, d, $J=11.9$ Hz, PhCH_2OC-5), 4.53 (1H, d, $J=12.4$ Hz, PhCH_2OC-6), 4.60 (1H, d, $J=11.9$ Hz, PhCH_2OC-5), 4.66 (2H, AB system, PhCH_2OC-1′), 4.70 (1H, d, $J=12.4$ Hz, PhCH_2OC-6), 5.26 (1H, dt, $J=9.7$, 4.8 Hz, *H*-10), 5.69 (1H, dd, $J=15.7$, 1.9 Hz, *H*-7), 5.71–5.80 (1H, m, *H*-8), 7.24–7.42 (15H, m, arom). ^{13}C NMR (100 MHz): δ 14.0 (*C*-7′), 22.6 (*C*-6′), 23.7 (br, *C*-4), 25.4 (*C*-3′), 28.9 (br, *C*-3), 29.4 (*C*-4′), 30.7 (*C*-2′), 31.8 (*C*-5′), 35.9 (*C*-9), 71.3 (Ph*C*H_2OC-5), 71.5 (Ph*C*H_2OC-6), 72.6 (Ph*C*H_2OC-1′), 76.4 (*C*-10), 77.3 (*C*-6), 78.3 (br, *C*-5), 79.7 (*C*-1′), 126.6 (*C*-8), 127.2, 127.4, 127.5, 128.0, 128.33, 128.35, 128.40, 131.6 (*C*-7), 138.4, 138.6, 138.8, 175.3 (*C*-2). IR (neat): ν_{max} 737, 978, 1027, 1072, 1120, 1148, 1222, 1274, 1377, 1454, 1496, 1737, 2856, 2932, 3030, 3064. MS, *m/z*: 571 ($[M+1]^+$, <0.1), 378 (0.8), 287 (3), 253 (11), 244 (1), 205 (2), 181 (9), 160 (5), 113 (4), 91 (100), 85 (5), 65 (2%). Anal. Calcd for $C_{37}H_{46}O_5$: C, 77.86; H, 8.12. Found: C, 77.94; H, 8.21.

4.2. Microcarpalide (1)

5,6,1′-*O*,*O*,*O*-Tribenzylmicrocarpalide (**14**) (23 mg, 0.040 mmol) was dissolved in dichloromethane (2 mL) and treated at 0 °C with a solution of titanium tetrachloride (53 μL, 0.484 mmol) in CH_2Cl_2 (0.5 mL). After stirring for 1 h, water (3 mL) was added to the turbid brown mixture. The organic phase was separated and the aqueous layer was extracted with CH_2Cl_2 (3×3 mL). The pooled organic phases were washed with satd $NaHCO_3$ (20 mL) and brine (20 mL), and dried over Na_2SO_4. After filtration and concentration in vacuo, the crude greenish-brown residue was purified by column chromatography on silica gel using AcOEt as the eluant, to afford a colourless viscous liquid (7 mg, 58% yield) whose spectral properties matched perfectly those reported in the literature for synthetic[5] and natural microcarpalide (**1**).[2]

Acknowledgements

Financial support from MIUR (COFIN 2003) and Università di Modena e Reggio Emilia ('Progetto Giovani Ricercatori' to P.D.) was greatly appreciated. Thanks are due to Adriano Benedetti and Maria Cecilia Rossi (Centro Interdipartimentale Grandi Strumenti) for spectroscopic assistance throughout the project. We are indebted to Stefano Baldini for preliminary experiments with halomethaneboronates **2a**,**c** and to Prof. Thomas Hemscheidt (Department of Chemistry, University of Hawai'i at Mānoa, Honolulu) for kindly sharing with us unpublished information about the endophytic fungal strain from which **1**[2] was originally isolated. We also thank the Fondazione Cassa di Risparmio di Modena for funding the purchase of the 400 MHz NMR spectrometer.

References and notes

1. (a) Giganti, A.; Friederich, E. The Actin Cytoskeleton as a Therapeutic Target: State of the Art and Future Directions. In *Progress in Cell Cycle Research*, Vol. 5; Meijer, L., Jézéquel, A., Roberge, M., Eds.; Kluwer: Amsterdam, 2003; pp 511–525. (b) Fenteany, G.; Zhu, S. *Curr. Top. Med. Chem.* **2003**, *3*, 593–616. (c) Rao, J. Y.; Li, N. *Curr. Cancer Drug Targets* **2004**, *4*, 267–283.
2. Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. *Org. Lett.* **2001**, *3*, 3479–3481.
3. Murga, J.; Falomir, E.; García-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447–3449.
4. Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873–2875.
5. Davoli, P.; Spaggiari, A.; Castagnetti, L.; Prati, F. *Org. Biomol. Chem.* **2004**, *2*, 38–47.
6. Banwell, M. G.; Loong, D. T. J. *Heterocycles* **2004**, *62*, 713–734.
7. Ishigami, K.; Kitahara, T. *Heterocycles* **2004**, *63*, 785–790.
8. (a) Matteson, D. S. *Acc. Chem. Res.* **1988**, *21*, 294–300. (b) Matteson, D. S. *Chem. Rev.* **1989**, *89*, 1535–1551. (c) Matteson, D. S. *J. Organomet. Chem.* **1999**, *581*, 51–65.
9. Reviews: (a) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (b) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830. (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (e) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**,

39, 2073–2077. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (g) Amstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388.
10. Fürstner, A. *Synlett* **1999**, 1523–1533.
11. Matteson, D. S.; Beedle, E. C. *Tetrahedron Lett.* **1987**, *28*, 4499–4502.
12. Whiting, A. *Tetrahedron Lett.* **1991**, *32*, 1503–1506.
13. Matteson, D. S.; Sadhu, M. K.; Peterson, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 810–819.
14. Hiscox, W. C.; Matteson, D. S. *J. Organomet. Chem.* **2000**, *614–615*, 314–317.
15. Ness, S.; Martin, R.; Kindler, A. M.; Paetzel, M.; Gold, M.; Jensen, S. E.; Jones, J. B.; Strynadka, N. C. J. *Biochemistry* **2000**, *39*, 5312–5321.
16. Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631–632.
17. Wuts, P. G. M.; Thompson, P. A. *J. Organomet. Chem.* **1982**, *234*, 137–141.
18. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH: Weinheim, 1987.
19. (a) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7588–7590. (b) Matteson, D. S.; Majumdar, D. *Organometallics* **1983**, *2*, 1529–1535.
20. (a) Midland, M. M.; Zolopa, A. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1979**, *101*, 248–249. (b) Matteson, D. S. *Acc. Chem. Res.* **1970**, *3*, 186–193.
21. (a) Matteson, D. S.; Ray, R. *J. Am. Chem. Soc.* **1980**, *102*, 7590–7591. (b) Matteson, D. S.; Ray, R.; Rocks, R. R.; Tsai, D. J. S. *Organometallics* **1983**, *2*, 1536–1543.
22. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 76–77.
23. Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069.
24. (a) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Riccardi Sirtori, F.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 681–684. (b) Caggiano, L.; Castoldi, D.; Beumer, R.; Bayón, P.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2003**, *44*, 7913–7919. (c) Beumer, R.; Bayón, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Riccardi Sirtori, F.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59*, 8803–8820.
25. Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 4525–4526.
26. Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.
27. (a) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett.* **2000**, *2*, 3731–3734. (b) Snider, B. B.; Song, F. *Org. Lett.* **2001**, *3*, 1817–1820.
28. Hemscheidt, T. Personal communication, February 2004.
29. (a) Rivero-Cruz, J. F.; García-Aguirre, G.; Cerda-García-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337–5344. (b) Rivero-Cruz, J. F.; Macías, M.; Cerda-García-Rojas, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511–514.
30. (a) Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34*, 999–1003. (b) Evidente, A.; Capasso, R.; Abouzeid, M. A.; Lanzetta, R.; Vurro, M.; Bottalico, A. *J. Nat. Prod.* **1993**, *56*, 1937–1943 (please note that the stereochemistry of pinolidoxin has since been revised by Fürstner's group).[23]
31. Diez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodriguez, F. *Synlett* **2003**, 1186–1188.
32. (a) Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953–1955. (b) Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Gullo, V.; Black, T.; Zhao, W.; Chan, T.-M.; McPhail, A. T. *J. Nat. Prod.* **2003**, *66*, 1527–1530.
33. Weber, D.; Sterner, O.; Anke, T.; Gorzalczancy, S.; Martino, V.; Acevedo, C. *J. Antibiot.* **2004**, *57*, 559–563.