Tetrahedron Letters 52 (2011) 7004–7007

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient and straightforward preparation of a building block for (−)-teubrevin G synthesis via chemically diversed oriented synthesis

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ARTICLE INFO

Article history:
Received 16 September 2011
Revised 17 October 2011
Accepted 19 October 2011
Available online 25 October 2011

Keywords:
Diversed oriented synthesis
Teubrevin G
Intramolecular coupling

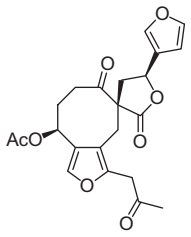
ABSTRACT

A rapid and efficient methodology to highly functionalised molecular units well suited as scaffolds for diversity-oriented molecular construction in the synthesis of natural products is reported herein. A key macrocyclic intermediate in the synthesis of the neo-clerodane diterpene (−)-teubrevin G was successfully synthesized in a 5-step sequence in a 70% overall yield using a novel intramolecular coupling between an allylborating agent and a 1,5-dialdehyde moiety.

The quest for new drugs has fostered the development of novel and simpler synthetic strategies that can grant access to highly complex molecules in a controllable fashion. Most of the emerging strategies are based on the paradigm of molecular complexity for the discovery of new chemical entities. Diversity oriented synthesis (DOS), natural products, and privileged structures based combinatorial libraries,[1–6] multicomponent reactions, and the latest introduced concept of Diverted total synthesis (DTS)[7,8] have been successfully utilized to fulfill the above mentioned paradigms.

There is an active search for new synthetic protocols which can address the modular and diversity-oriented construction of the aforementioned molecular complexity, particularly for oligosaccharides, glycoconjugates, diterpenoids, and so on. Clerodane diterpenes are particularly interesting due to their high structural diversities,[9–14] promising biological activities such as semiochemicals for insect repellents (antifeedants) as well as anti-inflammatory properties.[15–18] Many of these compounds have successfully been isolated from plants (mostly of the Lamiaceae family), microorganisms and/or marine organisms.[14,19,20] Many of these polyfunctionalised (neo)clerodane backboned diterpenes have certain structural motifs which include oxygenated 5-member rings as well as a characteristic decalin-type system.[21] However, there are interesting exceptions which are intrinsically different and thus possess unique structures and properties in terms of biological activities. One of such most relevant molecules is (−)-teubrevin G (Scheme 1). (−)-Teubrevin G **1** is a *neo*-clerodane diterpene which was originally isolated from the aerial part of *Teucrium brevifolium* (Lamiaceae).[22] Interestingly, it does not share the common features of most clerodane and *neo*-clerodane families, but comprises of an interesting carbon scaffold formed by a furan ring fused to an eight member macrocycle (specifically functionalized), bearing also a spiro chiral lactone. Such structural changes and peculiar chemical moieties as compared to similar diterpenes make this molecule highly interesting from a synthetic point of view (offering some advantages in terms of innovative synthetic strategies) as well as opening up a wide range of important studies concerning its unexplored biological activities.[21]

The full synthesis of (−)-teubrevin G was to date exclusively described some years back by Paquette et al.[23–25] However the



(-) Teubrevin G **1**

Scheme 1. Chemical structure of (−) teubrevin G, **1**.

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0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.10.112

formation of the key compound in the synthesis of 2,3,4-trisubstituted furan ring turned to be a really challenging step[26] that, although elegantly tackled, definitely required a more efficient and shorter way of preparation.[26]

In view of these premises, we sought to devise a more efficient protocol to synthesize a key building block for the synthesis of the *neo*-clerodane diterpene (−)-teubrevin G as well as the biological evaluation of all intermediate compounds in its synthesis.

The retrosynthetic plan for the synthesis of this chemical intermediate has been described in Scheme 2. Following a slightly modified chemistry to that performed by Roush,[27] the versatile intermediate **3** will be initially formed by vinylation-allylation of dialdehyde **4**. In principle, the synthesis will rely on two key steps. Firstly, the formation of 2,3,4-trisubstituted furan building block through efficient multicomponent domino reaction between methyl propiolate **6** and an aldehyde **7** (triggered by tributylphosphine as the nucleophile),[28] and secondly the double allylboration of a 1, 5-dialdehyde system via a novel intramolecular coupling.

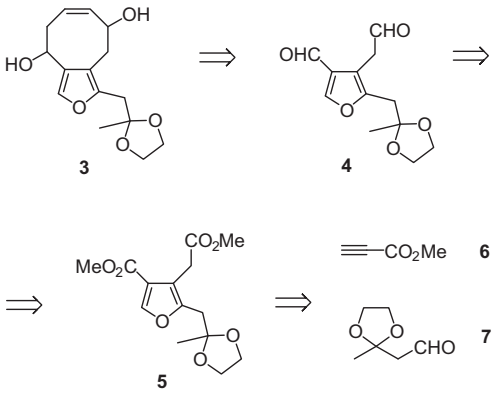
In order to match with our interest in the synthesis of new molecular entities bearing biological properties, we planned to tackle the diverted total synthesis (DTS) of (−)-teubrevin G with the intention to explore related derivatives that can be provided by the chemically versatile advanced intermediate **3** via conveniently selected chemistries (Fig. 1).

In light of these considerations, herein we report a novel synthetic approach to achieve the synthesis of the intermediate **3**, which can in principle grant us access to different structural analogs and eventually lead to the total synthesis of **1** (Scheme 3). A selective manipulation of various functionalities for the diversity sites D_n can potentially produce compound **3** congeners which could lead to synthetic molecules with improved pharmacokinetic properties and/or biological activities.

Initially, the versatile intermediate **3** was the target synthetic molecule. Its synthesis comprised a series of reactions as shown in Schemes 4–8.

In the first synthetic step, aldehyde **7** was prepared via condensation of β-ketoester **8** with ethyleneglycol and then selective reduction with DIBAL-H at −80 °C for 8 min, yielding 92% of the desired product (Scheme 4).[29]

Compound **5** was subsequently prepared by a multicomponent domino reaction between methyl propiolate **6** and aldehyde **7** (ratio 3:1) in the presence of catalytic amounts of tri-*n*-butylphosphine in chloroform at −60 °C followed by acid promoted aromatization to afford 2,3,4-trisubstituted furan (53% overall yield) as depicted in Scheme 5. Diester **5** was then completely reduced by treatment with $LiAlH_4$ to yield compound **11** and then it was selectively oxidized using MnO_2 as the catalyst in an overall yield of 83% (Scheme 6).[30]



Scheme 2. Synthetic plan to obtain advance intermediate **3**.

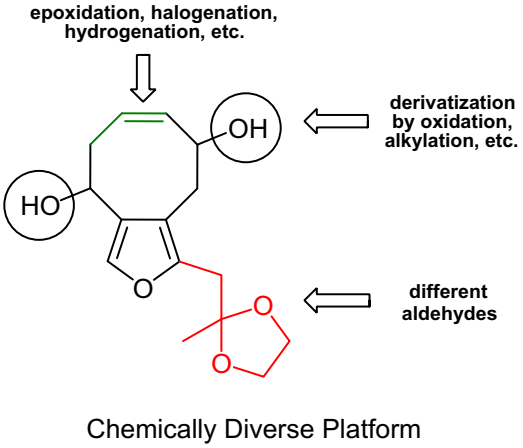
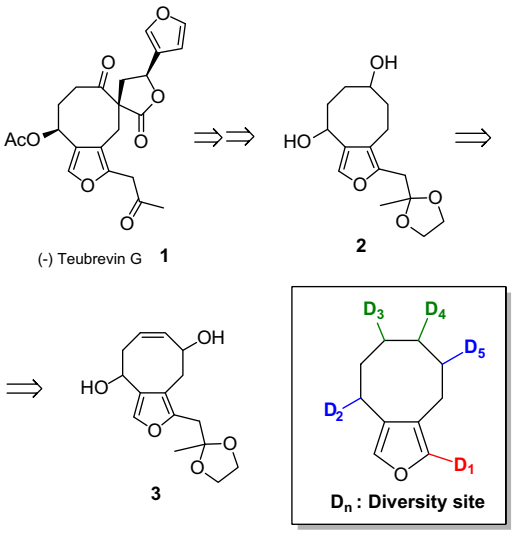
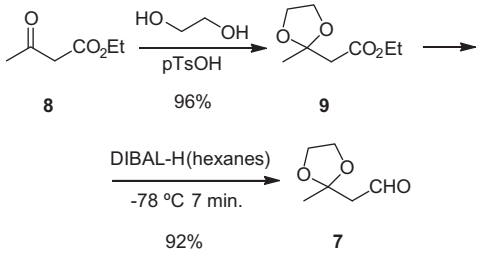


Figure 1. Reactivity pattern of the scaffold **3**.



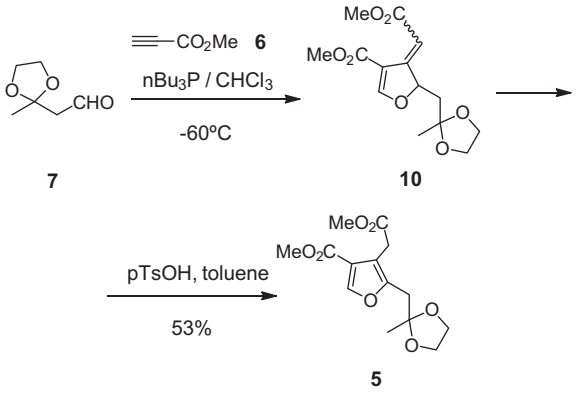
Scheme 3. Hypothetic retro-synthetic pathway to synthesize (−)-teubrevin G from intermediate **3** via functionalisation of diversity sites.



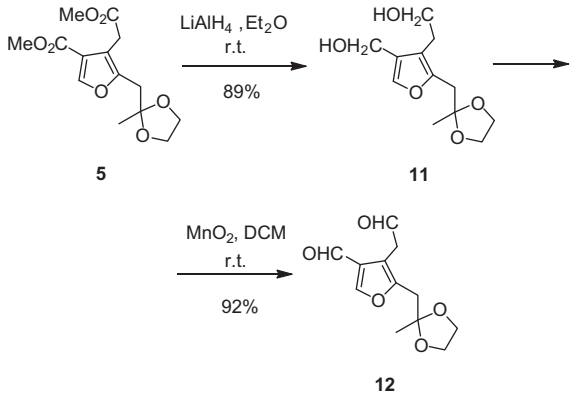
Scheme 4. Synthesis of dialdehyde **7**.

Subsequently, compound **8** was synthesized according to the Roush protocol[27] (Scheme 7), in which allenylmagnesium bromide **14** was added over an ethylether solution of **15** at −78 °C, yielding 60% of **16** along with magnesium salts. Then, **16** was transferred in situ with a cannula to a ethylether solution of ethylenglycolborane **17** at 0 °C, affording compound **18** (95% yield, based on **16**).

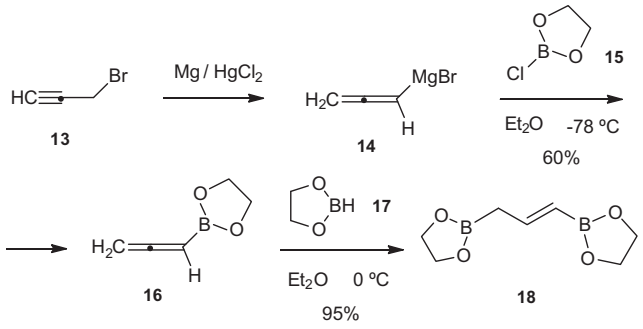
In our convergent approach, the synthesis of the eight-membered cycle was performed by a novel intramolecular coupling of dialdehyde **12** with the boryl-substituted allylboronate **18**



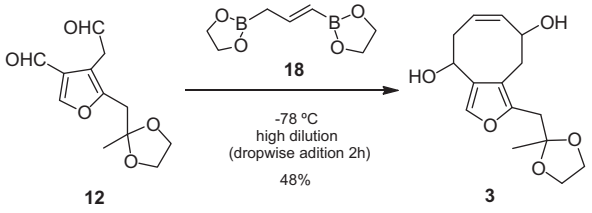
Scheme 5. Synthesis of diester **5**.



Scheme 6. Synthesis of dialdehyde **12**.

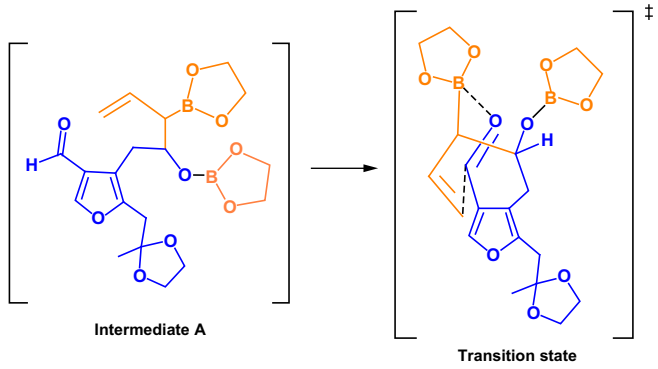


Scheme 7. Synthetic pathway to achieve γ-borinanyl-allylboronate **18**.



Scheme 8. Intramolecular coupling of γ-borinanyl-allylboronate **18** with dialdehyde **12** to afford compound **3**.

(Scheme 8). The double allylboration reaction was performed by slowly adding 1 equiv of allylboronating agent **18** for 2 h over 1 equiv of **12** in ethylether at −78 °C. The mixture was then allowed to stir at room temperature for 24 h. The crude product



Scheme 9. Hypothetic transition state of the coupling reaction of compound (**18**) with the 1,5-dialdehyde (**12**).

was subjected to standard oxidative workup (NaOH, H_2O_2) before product isolation, yielding 48% of the intermediate **3** upon chromatographic purification.

It is important to point out that compound **3** was obtained as a racemic mixture and its structural elucidation was determined using a two dimensional spectroscopic experiment (HMBC), which allowed us to establish proton-carbon correlation (See ESI).

The proposal formation mechanism of compound **3** was based on the different reactivity of the aldehyde groups. We concluded that the first coupling originated the adduct β-alkoxyallylboronate **A**, which spontaneously folds and reacts with the less reactive aldehyde group through a chair-type transition state (Scheme 9).

In summary, we have reported a facile access to the highly functionalized fragment **3** of (−)-teubrevin G (**1**), which was obtained in 5 steps and 70% overall yield, starting from cheap and commercially available compounds in a relatively simple and straightforward protocol. To the best of our knowledge, this is the first example of an intramolecular coupling between an allylboronating agent and a 1,5-dialdehyde structure for the generation of compound **3**. The evaluation of the biological activities of all compounds and the completion of the total synthesis of **1** will be reported in due course.

Experimental section

All chemicals were utilized as purchased unless otherwise stated. Product **5** was synthesized from **7** as described in Scheme 5. Tri-*n*-butylphosphine (0.44 mL, 1.72 mmol, 0.4 equiv) was added to a cooled solution (−60 °C) of methyl propiolate (1.13 mL, 12.7 mmol, 3 equiv) and **7** (550 mg, 4.23 mmol) in dry $CHCl_3$ (12 mL). The reaction mixture was stirred for 2 h and then quenched with HCl 5% (10 mL). After extraction with CH_2Cl_2 (3 × 10 mL), the organic layers were dried over anhydrous sodium sulfate. After the solvent had been removed at reduced pressure, products were purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 90:10) to yield **10** (53%) as a mixture of isomers (Z/E 1:2.9). A mixture of isomers of **10** (200 mg, 0.67 mmol) and toluene-4-sulfonic acid monohydrate (0.2 equiv) was dissolved in toluene (10 mL) and the resulting solution was heated to 90 °C. The reaction was monitored by TLC until the conversion was completed. The reaction mixture was loaded directly into a silica gel column and eluted with *n*-hexane/EtOAc 80:20 to yield **5** (187.5 mg, 92%) as an oil. IR (KBr, cm^{-1}): 3198.8, 2973.6, 2862.6, 1720.8, 1436. ^1H NMR (300 MHz, δ, $CDCl_3$): 1.49 (s, 3H), 2.69 (s, 2H), 3.51 (s, 2H), 3.64 (s, 3H), 3.79 (s, 3H), 3.96-4.17 (m, 4H), 7.69 (s, 1H). ^{13}C NMR (75 MHz, δ, $CDCl_3$): 21 (q), 32 (t), 40 (t), 49 (q), 51 (q), 64 (t), 65 (t), 106 (s), 115 (s), 122 (s), 144 (d), 152 (s), 160 (s), 168 (s). Anal. Calcd for $C_{14}H_{18}O_7$: %C 56.37; %H 6.08. Found: %C 56.12; %H 6.24.

Product **11** was synthesized from **5** as described in Scheme 6. A solution of $LiAlH_4$ (140 mg, 3.70 mmol, 2.2 equiv) in dry THF (5 mL) was added dropwise to a solution of **5** (500 mg, 1.67 mmol) in THF (3 mL) at room temperature for 1 h. The mixture was stirred for 4 h and then washed several times with a solution of ammonium sulfate (15 mL) and left under stirring overnight. The final solution was filtered through celite and extracted with EtOAc. Compound **11** was obtained as a yellowish oil (360 mg, 89% yield). The crude product was employed in the following reaction without purification. IR (KBr, cm^{-1}): 3397, 2972, 2870.6, 1723, 1452. ^1H NMR (300 MHz, δ, $CDCl_3$): 1.39 (s, 3H), 2.57 (s, 2H), 2.63–2.71 (t, J = 10 Hz, 2H), 3.65 (t, J = 8 Hz, 2H), 4.15–4.22 (m, 4H), 4.89 (s, 2H), 7.69 (s, 1H). ^{13}C NMR (75 MHz, δ, $CDCl_3$): 20 (q), 26 (t), 45(t), 56 (t), 61 (t), 63 (t), 65 (t), 108 (s), 118 (s), 121 (s), 137 (d), 149 (s). Anal. Calcd for $C_{12}H_{18}O_5$: %C 59.49; %H 7.49. Found: %C 59.52; %H 7.42.

Product **12** was synthesized from **11** as described in Scheme 6. MnO_2 (144 mg, 1.65 mmol, 20 equiv) was added to a solution of **5** (20 mg, 0.08 mmol) in dry dichloromethane (3 mL). The mixture was stirred for 48 h at room temperature, then filtered off through celite and washed with EtOAc. The organic layer was dried over anhydrous $MgSO_4$ and the solvent was evaporated in a rotary evaporator to yield compound **12** (17.6 mg, 92% yield) as an oil, without further chromatographic purification needed. IR (KBr, cm^{-1}): 3380.8, 2932, 2859, 1723.5, 1642, 1450. ^1H NMR (300 MHz, δ, $CDCl_3$): 1.42 (s, 3H), 2.59 (s, 2H), 3.46 (s, 2H), 3.64 (d, J = 11 Hz, 2H), 4.15–4.22 (m, 4H), 7.67 (s, 1H), 9.59 (s, 1H), 9.77–9.81 (t, J = 14 Hz, 1H). ^{13}C NMR (75 MHz, δ, $CDCl_3$): 21 (q), 36 (t), 43 (t), 64 (t), 66 (t), 109 (s), 111,(s) 132 (s), 149 (d), 154 (s), 184 (s), 200 (s). Anal. Calcd for $C_{12}H_{14}O_5$: %C 60.50; %H 5.92. Found: %C 60.38; %H 5.98.

Product **18** was synthesized from **16** as described in Scheme 7**:** A solution of **16** (ethylenglycolborane, 65.5 mg, 0.91 mmol) in dry Et_2O (5 mL) was added dropwise to a suspension of **17** (100 mg, 0.91 mmol) in dry Et_2O (3 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred until complete dissolution, indicating reaction completion. The solvent was evaporated in a rotary evaporator, yielding **18** (157 mg, 95%) as a transparent oil. The crude product was used in the next step without further chromatographic purification. IR (KBr, cm^{-1}): 3287.8, 2934.5, 2873.8, 1408.6. ^1H NMR (300 MHz, δ, $CDCl_3$): 1.22–1.27 (d, J = 8.25 Hz, 2H), 4.15 (s, 4H), 4.37 (s, 4H), 5.21–5.26 (d, J = 15.3 Hz, 1H), 6.57–6.62 (dt, J = 7.2 Hz, J = 15.3 Hz, 1H). ^{13}C NMR (75 MHz, δ, $CDCl_3$): 32 (t), 63 (t), 66 (t), 126 (d), 138 (d). Anal. Calcd for $C_7H_{12}B_2O_4$: %C 46.25; %H 6.65. Found: %C 46.23; %H 6.77.

Product **3** was synthesized from **12** as described in Scheme 8. A freshly prepared solution of **18** (13.63 mg, 0.075 mmol) in dry Et_2O (7 mL) was added dropwise (2 h) to a solution of **12** (18 mg, 0.075 mmol) in dry Et_2O (0.5 mL) under nitrogen atmosphere at −78 °C. The mixture was stirred for 2 h at −78 °C and then for 24 h at room temperature. The reaction flask was subsequently placed in an ice bath and a solution of NaOH 3 M (56 μL) was then added dropwise, followed by the addition of a solution of H_2O_2 50% (22 μL). The reaction was stirred vigorously for 4 h at room temperature. The extracts were washed with DCM (4 mL), a saturated solution of $NaHCO_3$ (2 mL) and another saturated solution of NaCl (2 mL). The aqueous phase was extracted with DCM and subsequently dried over anhydrous $MgSO_4$. The solvent was evaporated until dryness in rotavapor and the crude oil was purified by flash column chromatography (silica gel, *n*-hexane/EtOAc 7:3). Compound **3** was obtained as a colorless oil (10.1 mg, 48 %). IR (KBr, cm^{-1}): 3347, 2756, 1134, 752, 523. ^1H NMR (300 MHz, δ, $CDCl_3$): 7.60 (s, 1H), 5.67 (m, J=7.92 Hz, 1H), 5.53 (m, J = 16.3, 7.9 Hz, 1H), 4.85 (m, J = 12.2 Hz, 1H), 4.57 (m, 1H), 4.16 (m, 4H), 3.12 (d, J = 18 Hz, 2H), 2.75 (t, J = 12.5 Hz, 2H), 2.59 (s, 2H), 1.39 (s, 3H). ^{13}C NMR (75 MHz, δ, $CDCl_3$): 23 (q), 38 (t), 41 (t), 65 (t), 65.5 (t), 71 (d), 73 (d), 110 (s), 120 (s), 127 (s), 132 (d), 134 (d), 145 (d), 156 (s). Anal. Calcd for $C_{15}H_{20}O_5$: %C 64.27; %H 7.19. Found: %C 64.35; %H 6.98. More details of this compound including ^1H and ^{13}C NMR as well as HMDC spectra can be found in the ESI.

Acknowledgments

This research was supported by the Ministerio de Educación y Ciencia de España (MEC, SAF2006-06720). DGV acknowledges Gobierno de Canarias for a pre-doctoral fellowship. RL gratefully acknowledges Ministerio de Ciencia e Innovación for the concession of a Ramon y Cajal contract (RYC-2009-04199) and funding in the framework of project CTQ2011-28954-C02-02 as well as Consejeria de Ciencia e Innovacion, Junta de Andalucia for funding project P10-FQM-6711.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.112.

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