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Synthetic Studies toward the C32−C46 Segment of Hemicalide. Assignment of the Relative Configuration of the C36−C42 Subunit

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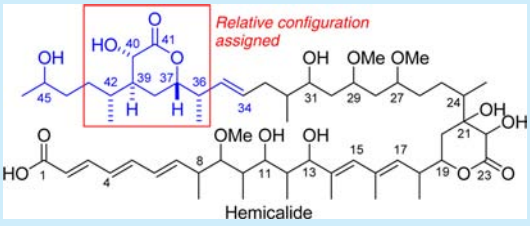
Supporting Information

ABSTRACT: The synthesis of five diastereomeric model compounds incorporating the C32−C46 segment of the antitumor marine natural product hemicalide has been achieved through a convergent approach relying on the 1,4-addition of an alkenyl boronate to an α,β-unsaturated δ-lactone followed by α-hydroxylation of an enolate and a Julia−Kocienski olefination. Comparison of the ^{1}H and ^{13}C NMR data of the model compounds with those of hemicalide enabled the assignment of the relative configuration of the C36−C42 subunit.



The discovery of antitumor agents acting by new mechanisms is of prime importance in cancer chemotherapy for the development of alternative or synergistic anticancer drugs, and in this context, natural products have always played a prominent role.[1] The naturally occurring complex polyketide hemicalide, recently isolated from extracts of the marine sponge *Hemimycale sp.* collected around the Torres Islands (Vanuatu), exhibits highly potent antiproliferative activity against several human cancer cell lines at subnanomolar concentrations.[2] The exact mechanism by which hemicalide disrupts the α/β microtubule network, as observed in immunocytochemistry assays,[2] is not yet fully understood, but its mode of action differs from the other well-known natural products targeting the mitotic spindle such as *Vinca* alkaloids or taxoids.[3] The new mode of action of hemicalide as a mitotic blocker, its extreme scarcity, and its challenging structure led us to embark in a research program devoted to the total synthesis of this marine natural product and simplified analogues thereof.

The planar structure of hemicalide was assigned by NMR spectroscopy, but the configuration of the 21 stereocenters contained in the 46 carbon atom backbone was initially unknown (Figure 1).[2] The relative configuration of the stereocenters embedded in the C8−C13 and C18−C24 segments of hemicalide was subsequently assigned by the synthesis of appropriate model compounds for the C1−C17 and C18−C25 subunits, combined with careful analysis and comparison of NMR spectra as well as computational conformational analysis.[4,5] These initial synthetic endeavors also resulted in the development of a convergent approach toward the C1−C25 fragment of hemicalide.[6] Herein, we report synthetic studies toward the yet unexplored C32−C46

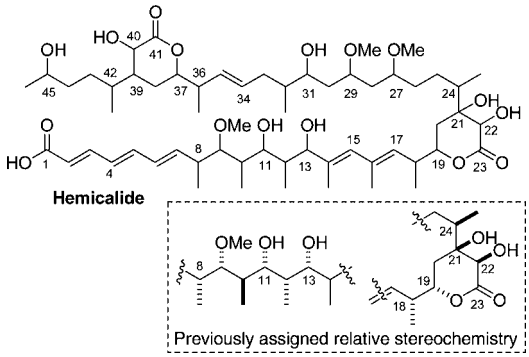


Figure 1. Structure of hemicalide.

segment of hemicalide and the assignment of the relative configuration of the α-hydroxy-δ-lactone C36−C42 subunit of this antitumor marine natural product.

The nuclear Overhauser effects (NOE) observed in the NOESY spectrum of hemicalide between H37 and the methyl group at C42, as well as with H40, enabled the determination of the relative configuration of the three stereocenters (C37, C39, and C40) in the δ-lactone ring.[7] To assign the relative configuration of the adjacent methyl-substituted stereocenters (C36 and C42) and possibly that of the C45 remote stereocenter, the synthesis of diastereomeric model compounds **A**, structurally related to the C32−C46 subunit, was undertaken with the goal of comparing their NMR data with those of hemicalide.[2] The C34−C35 disubstituted alkene in model

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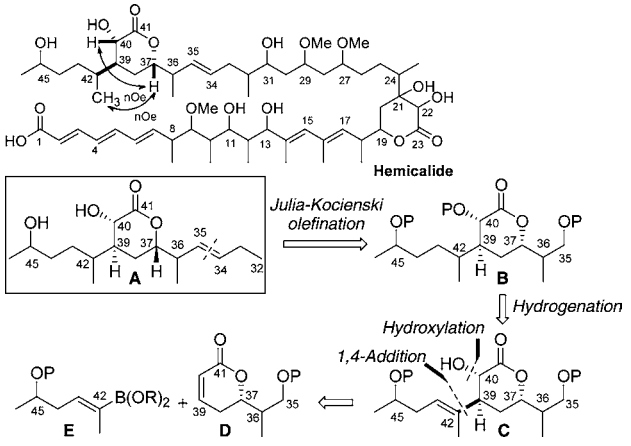
compound **A** would be formed by a Julia–Kocienski olefination applied to an aldehyde at C35, generated by oxidation of the corresponding protected primary alcohol in compound **B**. The introduction of the C42 stereocenter was envisaged by hydrogenation of the C42–C43 trisubstituted alkene **C**. This latter transformation, which may not proceed with high diastereocontrol, would provide an easy access to both epimers at C42 from a common precursor. The presence of an sp^2-hybridized carbon at C42 and the *trans* relative relationship of the substituents at C37, C39, and C40 in δ-lactone **C** further guided the retrosynthetic analysis. Installation of the hydroxyl at C40 would be achieved by a diastereoselective α-hydroxylation of a disubstituted lactone which, in turn, would result from the diastereoselective 1,4-addition of the trisubstituted alkenyl boronate **E** to the α,β-unsaturated δ-lactone **D**. This synthetic approach would be flexible as the configuration of C36, C37, and C45 could be initially varied in the coupling partners **D** and **E** and since both epimers would be later generated at C42, once the C39 and C40 stereocenters have been controlled (Scheme 1).

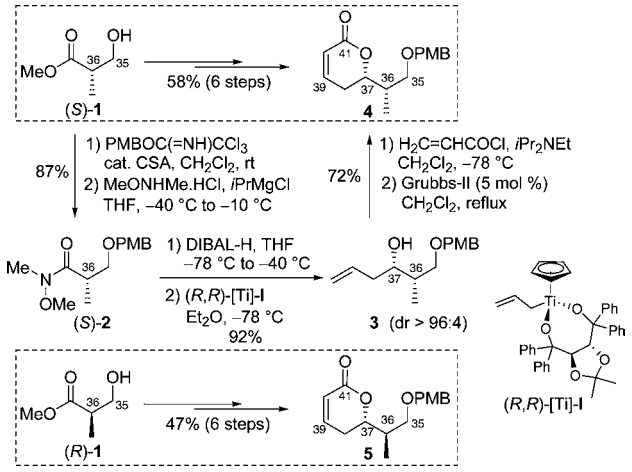
Scheme 1. Retrosynthetic Analysis of Model Compounds A



The synthesis of the two possible epimeric lactones **D** was achieved from both enantiomers of the Roche ester **1**. Enantiomer (*S*)-**1** was protected as a PMB ether and converted into the Weinreb amide **2** (87%) which was reduced with DIBAL-H.[8,9] The resulting aldehyde was engaged in a reagent-controlled face-selective allylation using Hafner–Duthaler's allyltitanium complex (*R*,*R*)-[Ti]-**I**[10] to provide homoallylic alcohol **3** (dr >96:4) in 92% yield. Acylation of **3** with acryloyl chloride followed by ring-closing metathesis in the presence of Grubbs' second-generation catalyst (Grubbs-II) provided the α,β-unsaturated δ-lactone **4** (72%, two steps from **3**).[11] Lactone **4** (C35–C41 subunit) was synthesized in six steps from (*S*)-**1** (58% overall yield), and application of a similar sequence[12] to enantiomer (*R*)-**1** afforded lactone **5** (47% overall yield) which is the epimer of **4** at C36 (Scheme 2).

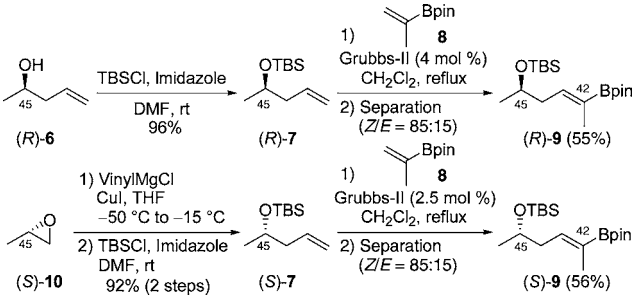
The enantiomers of alkenyl boronate **E** (C42–C46 subunit) were prepared from either commercially available (*R*)-pent-4-en-2-ol or (*S*)-propylene oxide. Protection of alcohol (*R*)-**6** as a TBS ether afforded (*R*)-**7** (96%) which was involved in a cross-metathesis with isopropenyl pinacol boronate **8**.[13] A mixture of geometric isomers (*Z*/*E* = 85:15) was obtained from which the major product (*R*)-**9** was isolated in 55% yield. Alternatively, ring opening of epoxide (*S*)-**10** with vinylMgCl in the presence of CuI followed by protection of the alcohol as a TBS ether

Scheme 2. Synthesis of α,β-Unsaturated δ-Lactones 4 and 5



afforded (*S*)-**7** (92%, two steps from (*S*)-**10**). Subsequent cross-metathesis with isopropenyl boronate **8** eventually produced the enantiomeric alkenyl boronate (*S*)-**9** (56%) (Scheme 3).

Scheme 3. Synthesis of Alkenyl Boronates (*R*)-9 and (*S*)-9



The coupling of the C35–C41 and C42–C46 subunits was then investigated. After a slight optimization, the 1,4-addition of the trisubstituted alkenyl boronate (*S*)-**9** to the α,β-unsaturated lactone **4** could be successfully carried out in the presence of $[Rh(COD)Cl]_2$ (3 mol %) and a stoichiometric quantity of LiOH in dioxane/H_2O (10:1) at 40 °C.[14] This reaction proceeded with moderate diastereoselectivity and produced lactones **11** and **11′** in an 83:17 ratio (74%).[15] Introduction of the hydroxyl group at C40 was achieved by enolization of the mixture of **11**/**11′** with NaHMDS followed by addition of Davis oxaziridine.[16] The trisubstituted lactone **12** was reproducibly obtained as a single diastereomer (72%) because the minor epimer **11′** did not undergo hydroxylation under these conditions. The relative configuration of **12** was unambiguously assigned by NMR spectroscopy (NOESY)[7] and confirmed that the 1,4-addition of alkenyl boronate (*S*)-**9** to lactone **4** occurred preferentially *trans* to the substituent at C37, whereas the hydroxyl group at C40 was subsequently introduced *trans* to the alkenyl residue at C39. The creation of the sixth stereocenter at C42 was then envisaged by hydrogenation of the trisubstituted C42–C43 alkene. Under an atmospheric pressure of hydrogen and in the presence of Pd/C, hydrogenation of **12** did not proceed. This transformation was achieved using an H-cube flow reactor under harsher conditions (Pd/C, 40 bar, 50 °C) to produce a mixture of epimeric lactones **13a**/**13b** (76%) with low diastereoselec-

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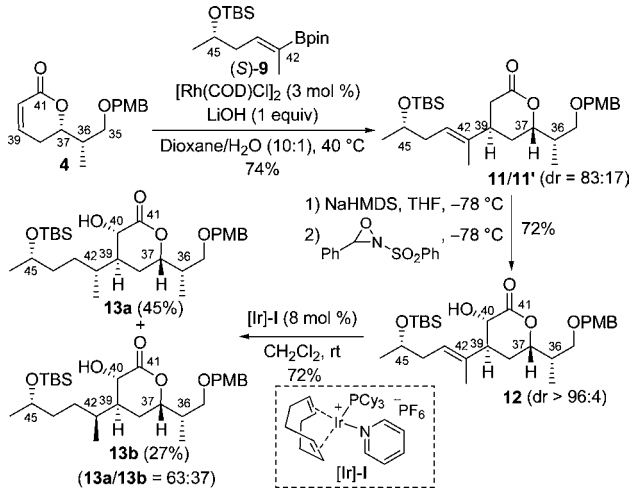
tivity (**13a**/**13b** = 45:55). It was envisaged to take advantage of the homoallylic alcohol at C40 and perform a directed reduction. In the presence of Crabtree's catalyst [Ir]-**I**,[17] hydrogenation of the C42−C43 alkene proceeded readily and led to a 63:37 mixture of lactones **13a**/**13b** presumably due to a lack of significant conformational restriction around the C39−C42 bond. Lactones **13a** (45%) and **13b** (27%) were separated by medium pressure liquid chromatography, and the absolute configuration at C42 was reliably assigned by Vibrational Circular Dichroism analysis of the corresponding epimers obtained after cleavage of the protecting groups (Scheme 4).[18]

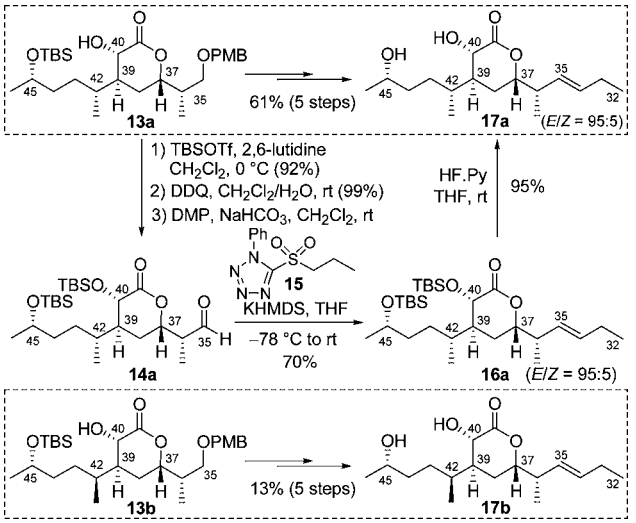
Scheme 4. Creation of the C39, C40, and C42 Stereocenters



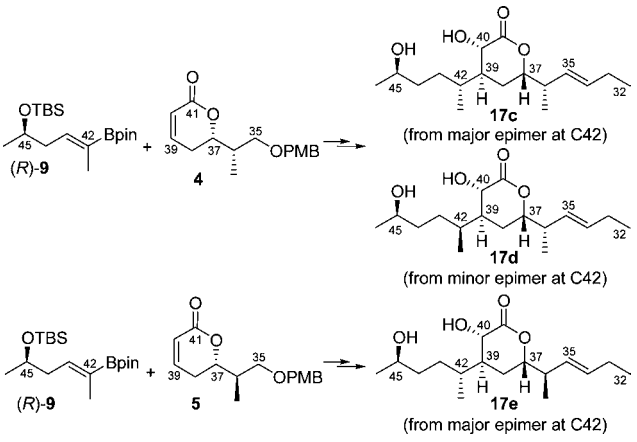
The next task was to install the C34−C35 disubstituted alkene in model compounds **A**. Protection of the alcohol at C40 in **13a** as a TBS ether followed by cleavage of the PMB ether led to a primary alcohol at C35 which was oxidized with Dess-Martin periodinane (DMP). The resulting aldehyde **14a** (92%, three steps from **13a**) was engaged in a Julia−Kocienski olefination[19] using sulfone **15** and KHMDS as the base which produced the disubstituted olefin **16a** (E/Z = 95:5) in 70% yield. Subsequent cleavage of the TBS ethers at C40 and C45 led to a first model compound **17a** for the C32−C46 subunit of hemicalide. Compound **13b** was engaged in the same sequence of reactions as described for **13a** that led to **17b** (13% overall yield, unoptimized), which is the epimer of **17a** at C42 (Scheme 5). Following the same strategy, lactones **17c** and **17d** which are the epimers at C45 of compounds **17a** and **17b**, respectively, were prepared from α,β-unsaturated lactone **4** and the enantiomeric alkenyl boronate (*R*)-**9**. Compound **17e**, which is the epimer of **17c** at C36, was also synthesized from lactone **5** and alkenyl boronate (*S*)-**9** (Scheme 6).[7]

The NMR spectra of **17a** and **17c**, as well as those of **17b** and **17d**, were nearly indistinguishable thereby preventing the configurational assignment of the remote C45 stereocenter.[7] Comparison of the ^{13}C NMR spectra of model compounds **17c**, **17d**, and **17e** with those of hemicalide turned out to be particularly informative (Figure 2).[7] For selected representative atoms leading to distinguishable signals, the best agreement with hemicalide was obtained with compound **17c** ($|\Delta\delta| \leq 0.5$ ppm) whereas significant deviations ($|\Delta\delta| > 4$ ppm) were observed for **17d** (epimer at C42) at C43 and the methyl group at C42 [Me(42)]. It is worth noting that the chemical shifts of C37, C36 and the methyl group at C36 [Me(36)] are similar in

Scheme 5. Model Compounds 17a and 17b



Scheme 6. Model Compounds 17c, 17d, and 17e



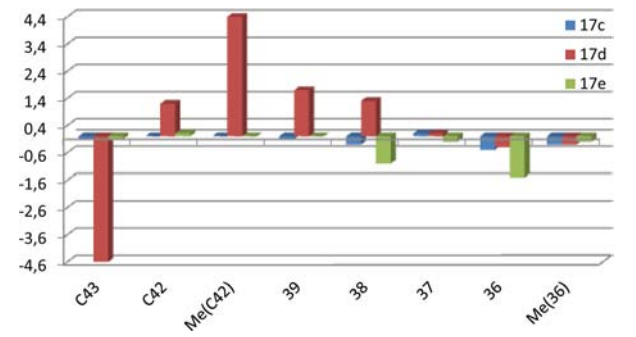


Figure 2. $\Delta\delta$ (ppm) between diastereomeric model compounds **17c**, **17d**, **17e** and hemicalide in ^{13}C NMR (CD_3OD).

17c and **17d** (epimers at C42) and, conversely, no significant variations are observed in the chemical shifts of the C43−C37 region for **17c** and **17e** (epimers at C36). This indicates that the modification of the configuration of C36 or C42 does not affect the chemical shifts of the atoms in the opposite chains (at C39 and C37, respectively) on the δ-lactone. Thus, it can be concluded that hemicalide has the same configuration at C42 as in model compounds **17c** and **17e**. Although C36 experienced a more pronounced upfield shift (−1.5 ppm) in **17e** than in **17c** (−0.5 ppm) relative to hemicalide, further discrimination was

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achieved by comparison of the ^{1}H NMR spectra (Figure 3).[7] Slight differences in chemical shifts ($\Delta\delta$) were observed between hemicalide and model compounds **17c**, **17d**, and **17e**. The best agreement was again observed for model compound **17c**, whereas the epimer at C36 **17e** led to a difference of 0.12 ppm for H37. Additionally, inspection of the signal corresponding to H37 was particularly meaningful. The splitting pattern observed in hemicalide (ddd, J = 11.0, 7.7, 3.5 Hz) is almost identical with that in **17c** (ddd, J = 11.0, 7.5, 3.9 Hz), is comparable to that in **17d** (ddd, J = 10.0, 7.5, 4.4 Hz), but is significantly different in the case of **17e** (dt, J = 11.1, 4.3 Hz), as a consequence of the conformational change induced by inversion of C36 in the latter compound. Thus, the relative configuration of the C36−C42 subunit of hemicalide appears to be the same as that in model compound **17c**.

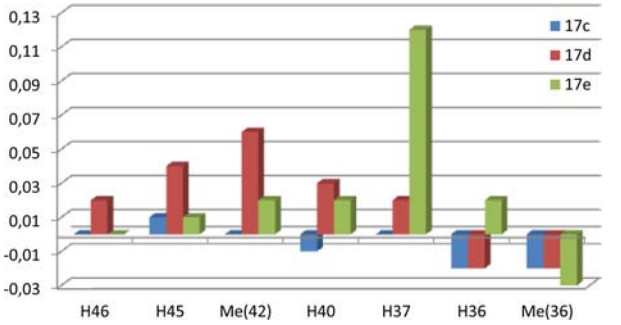

Figure 3. $\Delta\delta$ (ppm) between diastereomeric model compounds **17c**, **17d**, **17e** and hemicalide in ^{1}H NMR (CD_3OD).

In summary, comparison of the NMR data of five diastereomeric model compounds for the C32−C46 segment of hemicalide has allowed the assignment of the relative configuration of the C36−C42 δ-lactone subunit. These synthetic efforts also indicated the possibility to construct the C34−C35 olefin by a Julia−Kocienski olefination which will be exploited in our ongoing convergent total synthesis of this antitumor marine natural product and analogues thereof.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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