Enantioselective synthesis of natural products containing tertiary alcohols and contributions to a total synthesis of phorbasin B

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Chapter 5

Contributions to A Total Synthesis of Phorbasin B

In this chapter, efforts toward to the synthesis of phorbasin B are described. The skeleton of cyclohexenone with all needed three chiral centers was synthesized successfully.
5.1 Introduction

In 1994, the group of Kashman reported the isolation of four chlorinated phenylpyrrolyloxadiazoles, phorbazoles A-D, as first in class metabolites from sponges of the genus *Phorbas*.[1] Embodying an unprecedented chlorinated pyrrole moiety, these compounds represented a new class of marine alkaloids. One year later, two new potent cytostatic macrolides, phorboxazoles A and B, were isolated from the same species by Searle and Molinski.[2] The phorbazoles and the phorboxazoles were the only two accounts on isolation in the early stages of the research on *Phorbas* species until the discovery of the phorbasins. In 2000, Vuong and Capon isolated a novel unstable polyene diterpene from a southern Australian *Phorbas* species and named the compound phorbasin A[3] (Figure 1). In their ongoing investigations into the chemistry of southern Australian marine sponges they found another two phorbasin family members, phorbasin B and C, which displayed growth inhibitory activity against the Gram positive bacteria *Staphylococcus aureus* and *Micrococcus luteus*.[4] Recently, additional phorbasin members have been obtained, and studies have shown that this class of diterpenes possesses a range of specific cytotoxic properties.[5]

![Figure 1. Phorbasins and related structures](image)

5.2 The reported synthesis of phorbasin C

Structurally, the phorbasins are related to the terrestrial carvotacetone monoterpenes and carvone itself. Initially, the absolute stereochemistry of phorbasin B and C was depicted as in Figure 1 whereas the relative stereochemistry at C11 was not defined. In 2009, Micalizio completed the first total synthesis of (+)-phorbasin C and elucidated its structure[6] (Scheme 1). Starting from the chiral diene 1, they furnished the stereodefined diol 2. A subsequent, rather spectacular, titanium-mediated
reductive cross-coupling of 2 with TMS-propyne via a formal metallo-[3,3] rearrangement (A) afforded 1,4-diene 3 with exquisite selectivity after protonation of alkoxide B. 3 was further functionalized to vinyl iodide 7, the substrate for a subsequent Suzuki cross-coupling. In order to determine the stereochemistry at C11, the skeleton of the target molecule was assembled by Suzuki cross-coupling of 7 with both 8S and 8R, in turn prepared from 11R/11S by repetitive oxidation and olefination in several steps, to give compounds 9 and 10. This synthesis completed the structure elucidation of phorbasin C as \textit{ent}-10.

![Scheme 1. Total synthesis of (+)-phorbasin C](image)

5.3 Retrosynthesis of phorbasin B

In 2013, Y. Huang in our institute developed a novel catalytic asymmetric aproach to skipped dienes with a methyl-branched central stereocenter, using copper-catalyzed asymmetric allylic alkylation of diene bromides\(^7\) (Scheme 2). This system affords excellent regio- and enantioselectivity with a reasonable substrate scope. We realized that this method can provide a concise way to the synthesis of the side chain of the phorbasins, which encouraged us to design a novel approach to phorbasin B.
Scheme 2. Copper-catalyzed asymmetric allylic alkylation of diene bromides

Based on this idea, we retrosynthetically disconnected phorbasin B to substituted 2-cyclohexen-1-one 20 and 1,4-diene 21 (Figure 2), in the synthetic direction to be joined via a cross-methathesis reaction. In an initial synthetic approach in our department, Huang made a considerable effort towards the synthesis of ent-21 via a chiral TADDOL-titanium complex-catalyzed asymmetric Diels-Alder reaction\textsuperscript{[8]} of vinyl borate 16 and a dienol acetate 17 (Scheme 3).\textsuperscript{[9]} However, this Diels-Alder reaction was unsuccessful, and enforced the design of an alternative synthetic route.

Scheme 3. Huang’s attempt on the synthesis of ent-21 via D-A reaction.

In this new approach, we planned to prepare the 1,3-diene part of 21 by extending the hydroxymethyl group in 22. Compound 22, in turn, is a Rubottom/Baylis-Hillman product of cyclohexenone 23 (Figure 3). Compound 23 was expected to be the product of the intramolecular aldol condensation of keto-aldehyde 24, in turn derived, after functional group transformation, from the Evans aldol reaction product 25.
5.4. Results and discussion

The synthesis commenced with the preparation of chiral oxazolidinone 29 (Scheme 4). Acyl chloride 27 was treated with deprotonated (4S)-(−)-isopropyl-2-oxazolidinone 28 to give 29 in 87% yield.[10] The Evans aldol reaction of 29 and aldehyde 30, followed by an oxidative cleavage of the resulting borinate ester with H₂O₂ in methanol/aqueous phosphate buffer of pH 7[11] furnished the two desired chiral centers of product 32 as diastereomers (d.r. 82:18). The use of a phosphate buffer was essential to avoid elimination to the aldol condensation product. Then, reduction of 32 by LiBH₄ in THF/MeOH afforded a diastereomeric mixture of diol 25 in 90% yield. The protection of diol 25 was accomplished by acetal formation. Catalyzed by pyridinium p-toluenesulfonate, 25 reacted with benzaldehyde dimethyl acetal at room temperature[12] to give 33, together with a small amount of inseparable impurities but fortunately as one diastereomer because trans-25 did not react. Therefore the product was used as such in the next step. The Wacker oxidation of 33 with oxygen and PdCl₂/Cu(OAc)₂ in AcNMe₂/water at room temperature[13] afforded ketone 34 in a disappointing 38% yield over two steps from 25. The internal alkene of 34 was cleaved by ozonolysis and a subsequent intramolecular aldol condensation[14] of keto-aldehyde 24 resulted in the desired cyclohexenone 23 in 52% yield over two steps from 34.
To furnish the stereoselective α-hydroxylation of ketone 23 by Rubottom oxidation, initially triethylsilyl enol ether 35 was synthesized in 78% yield by treating 23 with TESOTf and Et$_3$N in CH$_2$Cl$_2$ (Scheme 5). Unfortunately, in the subsequent oxidation both dimethyl dioxirane (DMDO) and $m$-CPBA solely produced epoxide 36 in moderate yields without formation of the expected Rubbotom reaction product 38. In the $^1$H-NMR and $^{13}$C-NMR of 36, no diastereomer of 36 was detected. In the epoxidation of silyl enol ether 35, DMDO and $m$-CPBA attacked the opposite side of the [1,3]dioxinyl ring exclusively owing to the steric hindrance. To get to 38, the TES group was removed to afford α-hydroxy ketone 37 after rearrangement and the newly generated hydroxyl group was re-protected by treatment of 37 with TBSCl and imidazole in DMF at room temperature. Although 38 was synthesized this way successfully, the route is rather inefficient due to the low yields and the number of steps.
In a later stage of the research, we found that tert-butyldimethylsilyl enol ether 39 is a more suitable substrate for Rubottom reaction. 39 was prepared from 23 in 81% yield following a similar procedure as for 35 (Scheme 6). Oxidation of 39 with m-CPBA gave the desired rearrangement product 38 as well as a substantial amount of the corresponding deprotected product 37. An improved yield of 38 was obtained by treating 39 with DMDO in a mixture of acetone/CH₂Cl₂/water at room temperature. Employing these conditions, 38 was synthesized in a satisfying 64% yield together with 12% of 37 in one step from 39.

In the next step, we planned to introduce a hydroxymethyl group at C7 via Baylis-Hillman reaction. This reaction is initiated by conjugate addition of a suitable nucleophile, commonly used are dimethylamino pyridine (DMAP) and 1,4-diazabicyclo[2.2.2]octane (DABCO). The resulting enolate subsequently reacts with, in our case, formaldehyde and elimination of DMAP or DABCO then
provides the product. The conjugate addition of the nucleophile should on the one hand be favorable, to provide a sufficient concentration of the enolate, but on the other hand not suffer from direct addition of the nucleophile to the aldehyde and be reversible. These constraints have provided the Baylis-Hillman reaction with a dubious reputation in organic synthesis and long reaction times are often required. This was confirmed in the initial attempts, as 38 did not react with formaldehyde even over weeks (Table 1). To accelerate the Baylis-Hillman reaction, Ito and Iguchi in 2005 reported \[21\] the use of tributylphosphine and \(\text{Me}_2\text{PhP}\) in the reaction of 2-cyclopenten-1-one and 2-cyclohexen-1-one with aldehydes, and this provided the corresponding Baylis-Hillman products within a short time and in good yields (Scheme 7). The authors observed that the rate of the reaction was strongly dependent on the solvent and the optimal solvent combination in their hands was a mixture of MeOH, CHCl\(_3\), and water. With this catalytic system, the Baylis-Hillman reaction of 38 with formaldehyde (37% in H\(_2\)O) indeed afforded the desired primary alcohol 40 as the major product and 1,4-adduct 41 as a minor side product, the latter which unfortunately became the major product upon scale up. To suppress the formation of 41, the use of CHCl\(_3\) as the sole solvent (together with the water coming with the aqueous formaldehyde) was examined, which turned out to be very successful. Finally, employing this optimized system, 40 was obtained in 53% yield in a 2 d reaction with no 41 observed (Scheme 8). The primary alcohol of 41 was subsequently protected with a TBS-group to afford 42 in 94% yield.

![Scheme 7. The Baylis-Hillman reaction according to Ito and Iguchi](image)
The next step in the synthesis is the planned deprotection of the acetal in 42, preferably leaving a benzyl protecting group on the secondary alcohol. This however, turned out to be very difficult and we were not able to provide a satisfying protocol. Various conditions reported for the regioselective reductive ring opening, e.g. DIBAL,[22] BH3⋅THF in combination with Cu(OTf)2,[23] Pd(OH)2/C and H2, EtSH/Zn(OTf)2,[24] PDC/†BuOOH,[25] and TES/TFA,[26] were examined, but the desired product 22 was never observed and side products often appeared due to further reduction or deprotection of the TBS-protected alcohol. As the available time was consumed, the synthesis of phorbasin B was not further pursued from this point.

5.5 Conclusion
In summary, the three chiral centers in the cyclohexenone fragment of phorbasin B have been constructed efficiently via Evans aldol reaction and Rubottom oxidation. Wacker oxidation afforded the carbonyl group for phorbasin B while the subsequent ozonolysis and intramolecular aldol condensation resulted in the desired
cyclohexenone. Given the recent advances in the Wacker oxidation, the overall yield in this sequence might well be improved. Employing an optimized Baylis-Hillman reaction, hydroxymethylation of the cyclohexenone fragment was achieved successfully. Although a yield of 53%, might seem modest, the added complexity to the molecule in combination with a carbon-carbon bond formation compensates for the moderate yield.

As the selective deprotection of 42 is apparently not achievable, full deprotection of 42 under acidic conditions followed by selective protection/deprotection of the resulting hydroxyl groups might well bring a solution. An alternative could be the use of a more readily removable protecting group, for example a p-methoxy benzyl group that can be oxidatively cleaved.

Once the primary alcohol 22 is obtained, further functionalization to furnish the side chain of phorbasin B is envisioned through oxidation (to 43), alkynylation (to 44), Zr-catalyzed methylalumination/iodination (45) and finally Suzuki cross-coupling (to provide 21). In the final stages, metathesis of fragment 21 and the 1,4-diene 20 is planned to afford the natural product phorbasin B (Scheme 9).

Scheme 9. The planning for the remaining steps in the synthesis of phorbasin B

5.6 Experimental section

General remarks: $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a Varian AMX400 (400 and 100 MHz, respectively) with CDCl$_3$ as solvent. Chemical shifts were determined relative to the residual solvent peaks (CHCl$_3$, $\delta$ = 7.26 ppm for $^1$H-NMR, $\delta$ = 77.0 ppm for $^{13}$C-NMR). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL) at rt, with equals approximately 20 degrees. Thin-layer chromatography (TLC) was performed on Merck TLC Silica gel 60 Kieselguhr F254. Flash chromatography was performed on silica gel Merck Type 9385 230-400 mesh. All starting materials and chemical reagents were purchased from Aldrich, Acros and 102
(S)-4-(1-Methylethyl)-3-(1-oxo-4-pentenyl)-2-oxazolidinone (29). To a stirred mixture of 4-pentenoic acid 26 (9.3 mL, 91 mmol) and a few drops of DMF, oxalyl chloride (8.2 mL, 91 mmol) was slowly added at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 1 h to afford 4-pentenyl chloride 27.

To a stirred solution of (4S)-(−)-isopropyl-2-oxazolidinone 28 (10.0 g, 77.4 mmol) in dry THF (100 mL) was added NaH (3.7 g, 93 mmol, as a 60% dispersion in mineral oil) at 0 °C under nitrogen. The resulting mixture was stirred for 1 h and then was added 27 drop-wise. The reaction mixture was allowed to warm to rt and stirred overnight. Subsequently, the reaction was quenched by the addition of saturated NH₄Cl (aq) and the organic layer was separated. The aqueous layer was extracted with Et₂O and the combined organic phases were dried over anhydrous Na₂SO₄, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane : Et₂O = 3 : 1) to afford 29 (14.2 g, 87%) as a colorless oil. [α]₂⁰D = +823 (c 1.20, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 5.86-5.76 (m, 1 H), 5.07-4.94 (m, 2 H), 4.41-4.37 (m, 1 H), 4.26-4.15 (m, 2 H), 3.09-3.01 (m, 1 H), 2.98-2.88 (m, 1 H), 2.42-2.29 (m, 3 H), 0.87 (dt, J = 7.2 Hz, 2.8 Hz, 3 H), 0.83 (dt, J = 7.2 Hz, 2.8 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 154.0, 136.7, 115.5, 63.4, 58.3, 34.7, 28.34, 28.29, 17.9, 14.6; HRMS (ESI) calcd. for C₁₁H₁₈NO₃ [M + H]⁺ 212.1281, found 212.1273.

(S)-4-(1-Methylethyl)-3-((2S,3R)-2-allyl-3-hydroxy-5-methyl-1-oxo-4-hexenyl)-2-oxazolidinone (32). To a solution of 29 (14.2 g, 67 mmol) in dry CH₂Cl₂ (120 mL) was added dibutylboron triflate (74 mL, 74 mmol, 1 M in CH₂Cl₂) at 0 °C under nitrogen. The resulting solution was stirred for 15 min at 0 °C and then DIPEA (14.0 mL, 80.5 mmol) was added. The reaction mixture was stirred for an additional 1.5 h before cooling down to −78 °C. Then 3-methyl-2-butenal 30 (6.8 mL, 71 mmol) was added and the reaction mixture was stirred for 3 h before warming to rt. The resulting solution was stirred overnight at rt and quenched with phosphate buffer of pH 7. Then
a mixture of methanol / 30% aqueous H$_2$O$_2$ (150 mL, v/v = 2/1) was added to the mixture and the organic layer was separated after stirring vigorously for 1 h. The aqueous layer was extracted with CH$_2$Cl$_2$ and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated in vacuo.$^{[11]}$ The residue was purified by column chromatography on silica gel (pentane : CH$_2$Cl$_2$ = 3 : 1) to afford 32 (15.5 g, 78%) as white solid. $[^{13}]$$\text{[α]}_20^D = +43$ (c 0.89, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.85-5.75 (m, 1 H), 5.24 (dt, $J = 8.8$ Hz, 1.2 Hz, 1 H), 5.05 (dd, $J = 16.8$ Hz, 1.2 Hz, 1 H), 4.97 (d, $J = 10.4$ Hz, 1 H), 4.57 (dd, $J = 8.8$ Hz, 6.0 Hz, 1 H), 4.43-4.40 (m, 1 H), 4.30-4.25 (m, 1 H), 4.22-4.14 (m, 2 H), 2.52-2.43 (m, 3 H), 2.29-2.25 (m, 1 H), 1.70 (d, $J = 0.8$ Hz, 3 H), 1.65 (d, $J = 0.8$ Hz, 3 H), 0.87 (d, $J = 6.8$ Hz, 3 H), 0.82 (d, $J = 6.8$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 174.3, 154.1, 136.9, 135.3, 124.1, 116.9, 69.3, 63.1, 58.7, 47.7, 32.8, 28.3, 25.9, 18.4, 18.0, 14.6; HRMS (ESI) calcd. for C$_{16}$H$_{24}$NO$_3$ [M − OH]$^+$ 278.1751, found 278.1740.

(2R,3R)-2-Allyl-5-methylhex-4-ene-1,3-diol (25). To a solution of 32 (15.2 g, 51.5 mmol) in MeOH/THF (80 mL/80 mL) was added LiBH$_4$ (2.24 g, 103 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt and quenched with saturated NH$_4$Cl (aq). The solution was extracted with Et$_2$O and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane : Et$_2$O = 1 : 1) to afford 25 (7.9 g, 90%) as white solid. $[^{13}]$$\text{[α]}_20^D = +9$ (c 0.30, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.87-5.77 (m, 1 H), 5.36-5.33 (m, 1 H), 5.09-5.01 (m, 2 H), 4.57 (dd, $J = 9.2$ Hz, 4.4 Hz, 1 H), 3.77 (dd, $J = 11.2$ Hz, 7.2 Hz, 1 H), 3.67 (dd, $J = 11.2$ Hz, 4.4 Hz, 1 H), 2.27-1.96 (m, 5 H), 1.76 (d, $J = 1.2$ Hz, 3 H), 1.69 (d, $J = 1.2$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 136.9, 136.7, 124.4, 116.3, 71.2, 64.0, 45.2, 31.4, 26.0, 18.4; HRMS (APCI) calcd. for C$_{11}$H$_{17}$O [M − OH]$^+$ 153.1274, found 153.1273.

(4R,5R)-5-Allyl-4-(2-methylprop-1-en-1-yl)-2-phenyl-1,3-dioxane (33). To a solution of 25 (7.90 g, 46.4 mmol) in CH$_2$Cl$_2$ (100 mL) was added pyridinium p-toluenesulfonate (0.58 g, 2.3 mmol) and benzaldehyde dimethyl acetal (7.3 mL, 49
Contributions to a total synthesis of phorbasin B

mmol) at rt. The resulted mixture was stirred overnight and quenched with Et₃N.\[12\]
The solvent was removed under reduced pressure and the residue was purified by
column chromatography on silica gel (pentane : Et₂O = 30 : 1) to afford impure 33 (10 g)
and starting material (1.4 g). The obtained 33 was used for the next step without
further purification. \[\alpha\]₂₀° = +9.6 (c 1.36, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ
7.52-7.49 (m, 2 H), 7.38-7.30 (m, 3 H), 5.88-5.78 (m, 1 H), 5.60 (s, 1 H), 5.37 (dt, \(J =
8.0 \text{ Hz}, 1.2 \text{ Hz}, 1 \text{ H}\), 5.15 (dd, \(J = 16.8 \text{ Hz}, 1.2 \text{ Hz}, 1 \text{ H}\), 5.08 (d, \(J = 10.0 \text{ Hz}, 1 \text{ H}\),
4.78 (dd, \(J = 8.0 \text{ Hz}, 2.4 \text{ Hz}, 1 \text{ H}\), 4.24(dd, \(J = 11.6 \text{ Hz}, 1.2 \text{ Hz}, 1 \text{ H}\), 4.00 (dq, \(J =
11.6 \text{ Hz}, 1.2 \text{ Hz}, 1 \text{ H}\), 2.68-2.59 (m, 1 H), 2.44-2.38 (m, 1 H), 1.76 (s, 3 H), 1.72 (s, 3
H), 1.48 (dt, \(J = 10.8 \text{ Hz}, 1.2 \text{ Hz}, 1 \text{ H}\); \(^1\)C NMR (100 MHz, CDCl₃) δ 138.7, 137.3,
135.3, 128.8, 128.3, 126.2, 123.3, 116.7, 102.2, 77.7, 69.4, 38.1, 29.2, 25.9, 18.6;
HRMS (APCI) calcd. for C₁₇H₂₃O₂ [M + H]⁺ 259.1693, found 259.1693.

\(\text{(4R,5R)-4-(2-Methylprop-1-en-1-yl)-5-(2-oxopropyl)-2-phenyl-1,3-dioxane (34)}\)

To a solution of 33 (7.7 g from the previous step) in AcNMe₂/water (7 : 1, 160 mL) was
added PdCl₂ (528 mg, 3.0 mmol) and Cu(OAc)₂·H₂O (1.19 g, 6.0 mmol) and the
reaction flask was equipped with a balloon filled with oxygen. The reaction mixture
was stirred for 2 d at rt and subsequently diluted with ether. The organic layer was
separated and the aqueous layer was extracted with ether. The combined organic
phases were dried over anhydrous Na₂SO₄, filtered and evaporated \textit{in vacuo}.\[13\]
The residue was purified by column chromatography on silica gel (pentane : ether = 3 : 1)
to afford 34 (3.33 g, 38% over two steps) as a colorless oil. \[\alpha\]₂₀° = +3.4 (c 2.07,
CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ 7.51-7.48 (m, 2 H), 7.39-7.33 (m, 3 H), 5.58
(s, 1 H), 5.22 (dt, \(J = 7.2 \text{ Hz}, 1.2 \text{ Hz}, 1 \text{ H}\), 4.74 (dd, \(J = 7.2 \text{ Hz}, 2.4 \text{ Hz}, 1 \text{ H}\), 4.09 (d,
\(J = 1.6 \text{ Hz}, 2 \text{ Hz}, 1 \text{ H}\), 3.07 (dd, \(J = 18.8 \text{ Hz}, 9.6 \text{ Hz}, 1 \text{ H}\), 2.75 (dd, \(J = 18.4 \text{ Hz}, 3.2 \text{ Hz}, 1
H), 2.19 (s, 3 H), 2.16-2.13 (m, 1 H), 1.74 (s, 3 H), 1.70 (d, \(J = 1.2 \text{ Hz}, 3 \text{ H}\); \(^1\)C
NMR (100 MHz, CDCl₃) δ 208.3, 138.5, 136.2, 128.9, 128.3, 126.0, 122.8, 101.9,
77.4, 71.0, 39.5, 33.5, 30.6, 25.8, 18.7; HRMS (ESI) calcd. for C₁₇H₂₂O₃Na [M +
Na]⁺ 259.1693, found 259.1693.
(4S,5R)-4-Carbaldehyde-5-(2-oxopropyl)-2-phenyl-1,3-dioxane (24) Through a stirred solution of 34 (3.32 g, 12.1 mmol) in CH₂Cl₂ (30 mL) at −78 °C was bubbled ozone during 1 h until a blue color persisted. Subsequently, nitrogen was bubbled through the solution until the blue color had disappeared. Me₂S (5 mL) was added dropwise and the mixture was stirred at rt for 2 h. Volatiles were removed under reduced pressure and the residue (crude 24) was used in the next step without further purification.

(4aR,8aR)-2-Phenyl-4a,5-dihydro-4H-benzo[d][1,3]dioxin-6(8aH)-one (23) To a solution of 24 (from the previous step) in CH₂Cl₂ (80 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1.8 mL, 12 mmol) at rt. The resulted mixture was stirred overnight followed by addition of MsCl (2.8 mL, 36 mmol) and Et₃N (15 mL, 109 mmol). The reaction mixture was stirred for another 0.5 h and quenched with saturated NH₄Cl (aq). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and evaporated in vacuo. The residue was purified by column chromatography on silica gel (pentane : ether = 1 : 1) to afford 23 (1.44 g, 52% over two steps) as a yellow oil. [α]²⁰ D = −158 (c 0.85, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.51-7.48 (m, 2 H), 7.40-7.35 (m, 3 H), 6.93 (dd, J = 10.0 Hz, 5.6 Hz, 1 H), 6.19 (d, J = 10.0 Hz, 1 H), 5.60 (s, 1 H), 4.56 (dd, J = 5.6 Hz, 2.8 Hz, 1 H), 4.24 (dd, J = 12.0 Hz, 3.2 Hz, 1 H), 4.08 (d, J = 12.0 Hz, 1 H), 3.23 (dd, J = 16.4 Hz, 13.6 Hz, 1 H), 2.45 (dd, J = 16.4 Hz, 4.0 Hz, 1 H), 2.08 (dd, J = 13.6 Hz, 4.0 Hz, 1 H); ¹³C NMR (100 MHz, CDCl₃) δ 199.7, 142.7, 137.7, 132.7, 129.2, 128.4, 126.1, 101.9, 70.6, 70.0, 37.1, 32.6; HRMS (ESI) calcd. for C₁₄H₁₃O₃ [M + H]⁺ 231.1016, found 231.1007.
**Triethyl(((4aR,8aR)-2-phenyl-4a,8a-dihydro-4H-benzo[d][1,3]dioxin-6-yl)oxy)silane (35)** To a solution of 23 (203 mg, 0.88 mmol) in CH$_2$Cl$_2$ (10 mL) were added Et$_3$N (0.15 mL, 1.06 mmol) and TESOTf (0.24 mL, 1.06 mmol) at 0 °C. The resulting mixture was warmed to rt and stirred for 0.5 h. The reaction was quenched with saturated NH$_4$Cl (aq) and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated *in vacuo*.\textsuperscript{[15]} The residue was purified by column chromatography on silica gel (pentane : ether = 15 : 1) to afford 35 (236 mg, 78%) as a colorless oil. \([\alpha]^{20}_D = -178\ (c 0.64, \text{CHCl}_3); \) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.46-7.43 (m, 2 H), 7.33-7.31 (m, 3 H), 6.10 (dd, $J = 9.6$ Hz, 2.0 Hz, 1 H), 6.02 (d, $J = 9.6$ Hz, 5.6 Hz, 1 H), 5.47 (s, 1 H), 5.07 (t, $J = 1.2$ Hz, 1 H), 4.31 (td, $J = 5.2$ Hz, 1.2 Hz, 1 H), 4.242-4.235 (m, 2 H), 2.35 (t, $J = 2.0$ Hz, 1 H), 1.02 (t, $J = 8.0$ Hz, 9 H), 0.74 (q, $J = 8.0$ Hz, 6 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.6, 138.5, 131.4, 128.9, 128.2, 126.3, 124.2, 106.8, 100.5, 70.7, 69.4, 34.8, 6.7, 4.9; HRMS (ESI) calcd. for C$_{20}$H$_{29}$O$_3$Si [M + H]$^+$ 345.1881, found 345.1875.

**Triethyl(((1aS,3aR,7aR,7bS)-5-phenyl-3a,7a,7b-tetrahydro-1aH-oxireno[2',3':3,4]benzo[1,2-d][1,3]dioxin-1a-yl)oxy)silane (36)** To a solution of 35 (82 mg, 0.24 mmol) in CH$_3$CN/DME (dimethoxyethane) (3 mL, 2 : 1) were added Bu$_4$NHSO$_4$ (3.9 mg, 0.012 mmol), acetone (0.64 mL, 8.7 mmol) and 0.1 M K$_2$CO$_3$ (0.58 mL). Oxone (533 mg, 0.87 mmol in 2.3 mL 4 × 10$^{-4}$ M EDTA solution) and K$_2$CO$_3$ (533 mg, 3.86 mmol in 2.3 mL H$_2$O) were added separately by syringe pump over 1.5 h at rt. The reaction mixture was stirred for 2 h and subsequently extracted with ether. The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and evaporated *in vacuo*.\textsuperscript{[16]} The residue was purified by column chromatography on silica gel (pentane : ether = 5 : 1) to afford 36 (42 mg, 49%) as a colorless oil. \([\alpha]^{20}_D = -149\ (c 0.50, \text{CHCl}_3); \) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50-7.48 (m, 2 H), 7.40-7.36 (m, 3 H), 6.81 (dd, $J = 9.6$ Hz, 5.2 Hz, 1 H), 6.14 (d, $J = 9.6$ Hz, 1 H), 5.63 (s, 1 H), 4.91 (d, $J =
12.0 Hz, 1 H), 4.69 (dd, J = 5.2 Hz, 2.8 Hz, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.02 (dd, J = 12.0 Hz, 2.8 Hz, 1 H), 1.97 (d, J = 11.2 Hz, 1 H), 1.02 (t, J = 8.0 Hz, 9 H), 0.78-0.71 (m, 6 H); 13C NMR (100 MHz, CDCl3) δ 199.5, 141.4, 137.8, 131.3, 129.2, 128.4, 126.1, 102.4, 72.2, 71.2, 66.9, 40.3, 6.8, 4.9; HRMS (ESI) calcd. for C20H29O4Si [M + H]+ 361.1830, found 361.1825.

**tert-Butyldimethyl(((4aR,8aR)-2-phenyl-4a,8a-dihydro-4H-benzo[d][1,3]dioxin-6-yl)oxy)silane (39)** 39 was prepared from 23 in 81% yield based on recovered starting material according to a procedure for the preparation of 35. [α]20\textdegree = -165 (c 0.33, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.45-7.43 (m, 2 H), 7.35-7.30 (m, 3 H), 6.07 (dd, J = 10.0 Hz, 1.6 Hz, 1 H), 6.01 (dd, J = 10.0 Hz, 5.2 Hz, 1 H), 5.47 (s, 1 H), 5.06 (s, 1 H), 4.33-4.30 (m, 1 H), 4.242-4.238 (m, 2 H), 2.35 (s, 1 H), 0.96 (s, 9 H), 0.21 (s, 6 H); 13C NMR (100 MHz, CDCl3) δ 148.7, 138.5, 131.5, 128.9, 128.2, 126.3, 124.2, 107.1, 100.5, 70.7, 69.4, 34.8, 25.7, 18.1, -4.4, -4.5; HRMS (ESI) calcd. for C20H29O3Si [M + H]+ 345.1881, found 345.1883.

(4aR,5S,8aR)-5-((tert-Butyldimethylsilyl)oxy)-2-phenyl-4a,5-dihydro-4H-benzo[d][1,3]dioxin-6(8aH)-one (38) To a solution of 39 (1.0 g, 2.9 mmol) in CH2Cl2/acetone (38 mL, 1 : 1) were added 18-crown-6 (77 mg, 0.29 mmol) and NaHCO3 (1.16 g, 13.8 mmol in 15 mL water). The resulting mixture was cooled to 0 °C followed by addition of oxone (2.10 g, 3.42 mmol in 10 mL H2O). The reaction mixture was warmed to rt and stirred for 2 h before quenching with saturated Na2S2O3 (aq) and NaHCO3 (aq). The mixture was subsequently extracted with CH2Cl2 and the combined organic phases were dried over anhydrous Na2SO4, filtered and evaporated in vacuo.[18] The residue was purified by column chromatography on silica gel (pentane : ether = 5 : 1 to 1 : 1) to afford 38 (664 mg, 64%) and 37 (85 mg, 12%) as colorless oils. 38: [α]20\textdegree = -182 (c 0.94, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.50-7.48 (m, 2 H), 7.40-7.36 (m, 3 H), 6.81 (dd, J = 10.0 Hz, 5.2 Hz, 1 H), 6.14 (d, J = 10.0 Hz, 1 H), 5.63 (s, 1 H),
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4.90 (d, J = 11.6 Hz, 1 H), 4.70 (dd, J = 5.6 Hz, 3.2 Hz, 1 H), 4.65 (d, J = 12.0 Hz, 1 H), 4.02 (dd, J = 12.0 Hz, 2.4 Hz, 1 H), 1.99 (ddd, J = 11.6 Hz, 2.4 Hz, 2.0 Hz, 1 H), 0.98 (s, 9 H), 0.23 (s, 3 H), 0.14 (s, 3 H); 13C NMR (100 MHz, CDCl3) δ 199.5, 141.4, 137.8, 131.3, 129.2, 128.4, 126.1, 102.3, 72.3, 71.4, 66.8, 40.3, 25.9, 18.6, -4.3, -5.6; HRMS (ESI) calcd. for C20H28O4SiNa [M + Na]+ 383.1649, found 383.1644.

(4aS,5S,8aR)-5-Hydroxy-2-phenyl-4a,5-dihydro-4H-benzo[d][1,3]dioxin-6(8aH)-one (37): [α]20 D = −138 (c 1.15, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.52-7.50 (m, 2 H), 7.41-7.36 (m, 3 H), 6.95 (dd, J = 10.0 Hz, 5.6 Hz, 1 H), 6.28 (d, J = 10.0 Hz, 1 H), 5.64 (s, 1 H), 4.87 (d, J = 12.0 Hz, 1 H), 4.71-4.67 (m, 2 H), 4.00 (dd, J = 12.4 Hz, 2.8 Hz, 1 H), 3.48 (br s, 1 H), 1.91-1.87 (m, 1 H); 13C NMR (100 MHz, CDCl3) δ 200.7, 143.8, 137.6, 129.6, 129.2, 128.3, 126.1, 102.2, 71.4, 69.4, 66.8, 39.7; HRMS (ESI) calcd. for C14H15O4 [M + H]+ 247.0965, found 247.0958.

(4aR,5S,8aR)-5-((tert-Butyldimethylsilyl)oxy)-7-(hydroxymethyl)-2-phenyl-4a,5-dihydro-4H-benzo[d][1,3]dioxin-6(8aH)-one (40). To a solution of 38 (210 mg, 0.58 mmol) in CHCl3 (4 mL) were added formaldehyde (0.10 mL, 1.3 mmol, 37% in water) and Bu3P (0.05 mL, 0.20 mmol) at rt.[21] The reaction mixture was stirred at room temperature for 2 d (in case the reaction ceased, more Bu3P was added) and purified directly by column chromatography on silica gel (pentane : ether = 1 : 1) to afford 40 (120 mg, 53%) as a colorless oil. [α]20 D = −135 (c 0.54, CHCl3); 1H NMR (400 MHz, CDCl3) δ 7.50-7.47 (m, 2 H), 7.41-7.35 (m, 3 H), 6.79 (d, J = 5.6 Hz, 1 H), 5.64 (s, 1 H), 4.91 (d, J = 11.6 Hz, 1 H), 4.74 (dd, J = 5.6 Hz, 3.2 Hz, 1 H), 4.62 (d, J = 12.0 Hz, 1 H), 4.41 (d, J = 14.4 Hz, 1 H), 4.24 (d, J = 14.4 Hz, 1 H), 4.02 (dd, J = 12.0 Hz, 2.8 Hz, 1 H), 2.01 (ddd, J = 11.6 Hz, 2.8 Hz, 2.0 Hz, 1 H), 0.98 (s, 9 H), 0.22 (s, 3 H), 0.14 (s, 3 H); 13C NMR (100 MHz, CDCl3) δ 200.6, 140.3, 137.8, 136.9, 129.2, 128.4, 126.1, 102.3, 71.7, 71.3, 66.9, 61.1, 40.3, 25.9, 18.5, -4.3, -5.5; HRMS (ESI) calcd. for C21H30O5SiNa [M + Na]+ 413.1755, found 413.1750.
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hyl)-2-phenyl-4a,5-dihydro-4\textit{H}-benzo[\textit{d}][1,3]dioxin-6(8\textit{aH})-one (41). To a solution of 40 (325 mg, 0.83 mmol) in CH₂Cl₂ (8 mL) were added imidazole (68 mg, 1.0 mmol) and TBSCl (138 mg, 0.92 mmol). The resulted mixture was stirred for 2 h at rt and quenched with water. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂. The combined organic phases were dried over anhydrous Na₂SO₄, filtered and evaporated \textit{in vacuo}. The residue was purified by column chromatography on silica gel (pentane : ether = 20 : 1) to afford 41 (394 mg, 94%) as a colorless oil. \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.51-7.49 (m, 2 H), 7.41-7.35 (m, 3 H), 6.87 (d, \(J = 6.0\) Hz, 1 H), 5.64 (s, 1 H), 4.90 (d, \(J = 11.6\) Hz, 1 H), 4.74 (t, \(J = 2.8\) Hz, 1 H), 4.62 (d, \(J = 12.0\) Hz, 1 H), 4.49 (dt, \(J = 16.4\) Hz, 2.0 Hz, 1 H), 4.29 (dd, \(J = 16.4\) Hz, 2.0 Hz, 1 H), 4.01 (dd, \(J = 12.4\) Hz, 2.8 Hz, 1 H), 1.99 (ddd, \(J = 11.6\) Hz, 2.4 Hz, 2.0 Hz, 1 H), 0.98 (s, 9 H), 0.90 (s, 9 H), 0.22 (s, 3 H), 0.13 (s, 3 H), 0.60 (d, \(J = 1.2\) Hz, 6 H); \(^13\)C NMR (100 MHz, CDCl₃) \(\delta\) 199.5, 141.1, 137.9, 135.0, 129.2, 128.4, 126.2, 102.3, 71.8, 71.3, 67.0, 59.6, 40.5, 25.9, 18.6, 18.3, -4.3, -5.49, -5.50, -5.6; HRMS (ESI) calcd. for C₂₇H₄₅O₅Si₂ [M + H]+ 505.2800, found 505.2791.

5.7 References


