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Toward the total synthesis of phorboxazole A: synthesis of an advanced C4–C32 subunit using the Jacobsen hetero Diels–Alder reaction

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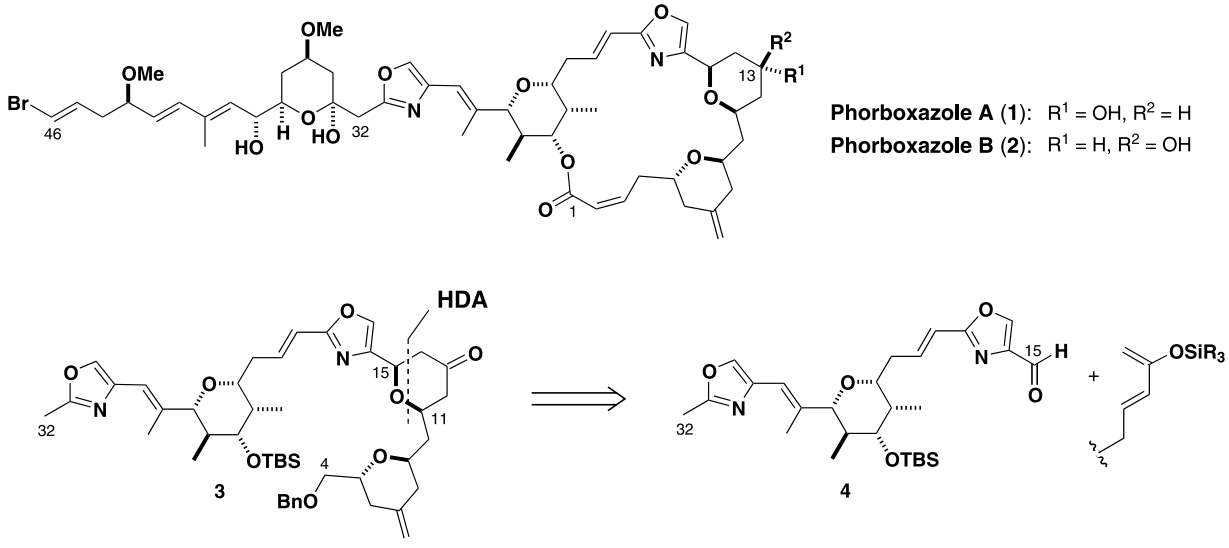
Abstract—The tetrahydropyranone **3**, representing a pentacyclic C_4–C_{32} segment of the phorboxazoles, was obtained by a complex hetero Diels–Alder (HDA) coupling performed between the 2-siloxydiene **23** and the oxazole aldehyde **4**, mediated by the chiral tridentate Cr(III) catalyst **14**. In preliminary studies, the tetrahydropyrans **17**, **33** and **35** were accessed using this same asymmetric HDA methodology with varying stereoselectivity.

Phorboxazoles A (**1**, Scheme 1) and B (**2**) were isolated by Searle and Molinski[1] from the Indian Ocean sponge *Phorbas* sp. endemic to the western coast of Australia. Both C_{13} epimers were found to be potent cytostatic agents with a mean GI_{50} <0.79 nM against the US NCI panel of 60 human cancer cell lines. The ability of the phorboxazoles to halt the cell cycle in S-phase provides a potential complement to the tubulin-mediated activity of antimitotic agents causing cell cycle arrest in the G_2/M phase. Owing to the significant structural complexity of these marine macrolides, their powerful biological activity and scarcity, the phorboxazoles have attracted considerable synthetic interest, leading to elegant total syntheses by Forsyth,[2] Evans[3] and Smith,[4] as well as to the preparation of various structural fragments by other groups.[5,6]



Scheme 1.

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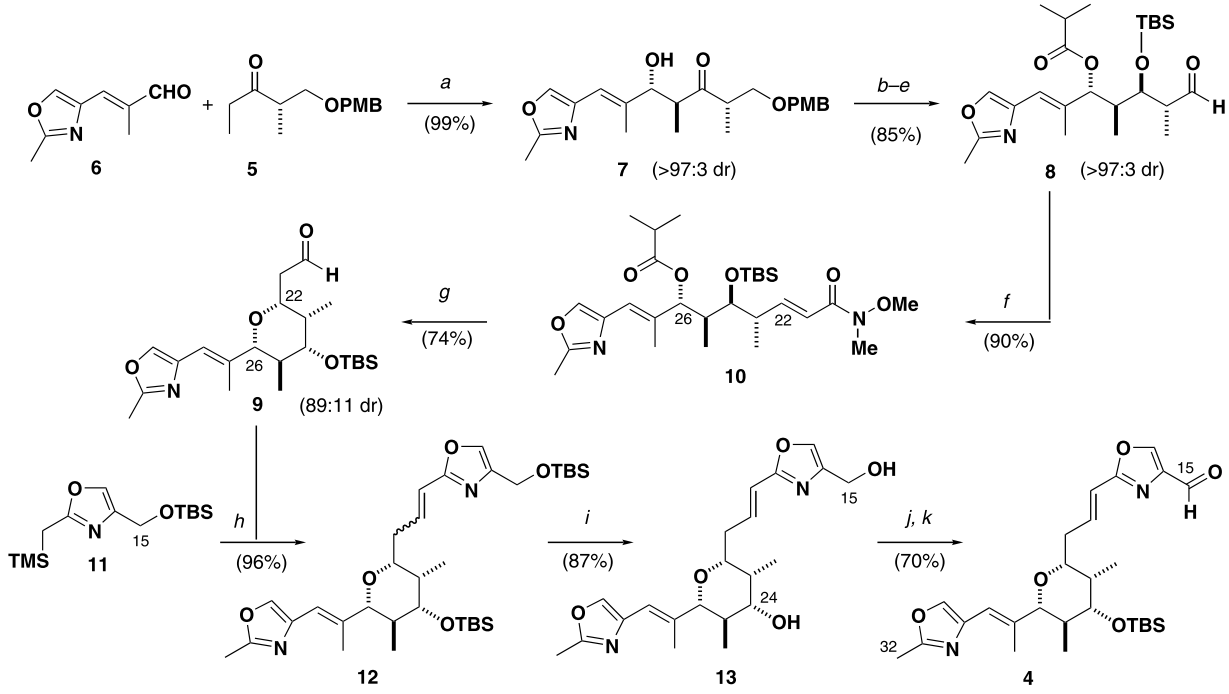
As part of studies towards the synthesis of phorboxazole A, we have previously outlined our strategy and reported the synthesis of a tricyclic C_{15}–C_{32} subunit.[6] We now report our latest efforts toward the preparation of a more advanced pentacyclic C_4–C_{32} subunit **3**, incorporating three of the four tetrahydropyrans and the two oxazole rings present in the phorboxazole structure. This novel approach relies on the use of an intact oxazole aldehyde, such as **4**, in the assembly of the C_{11}–C_{15} *cis*-tetrahydropyranone ring by an asymmetric hetero Diels–Alder (HDA) coupling reaction.

A highly stereocontrolled construction of the C_{15}–C_{32} aldehyde **4**, featuring the pentasubstituted tetrahydropyran and both 2,4-substituted oxazole rings of the phorboxazoles, as required for examining the pivotal asymmetric HDA coupling step, followed the sequence outlined in Scheme 2. This relied on a boron-mediated aldol reaction[6,7] between ketone **5** and aldehyde **6** to generate the *anti*,*anti*-adduct **7** (99%; >97:3 dr), which was subsequently elaborated over a four-step sequence into the aldehyde **8** by making use of an Evans–Tishchenko reduction (SmI_2, ^{i}PrCHO).[8] To configure the 2,6-*cis*-tetrahydropyran ring in aldehyde **9**, an improved procedure was developed for performing an intramolecular Michael-type reaction with an in situ generated enal. Homologation of **8** by a HWE reaction[9a] using the phosphonate reagent of Nuzillard[9b] gave the (*E*)-unsaturated Weinreb amide **10** (90%). Treatment of **10** with excess DIBAL (7 equiv.) in toluene, followed by an acidic work-up, then led to diastereoselective conjugate addition of the liberated C_{26} hydroxyl group to form aldehyde **9**, as a separable 8.3:1 mixture of C_{22} epimers.

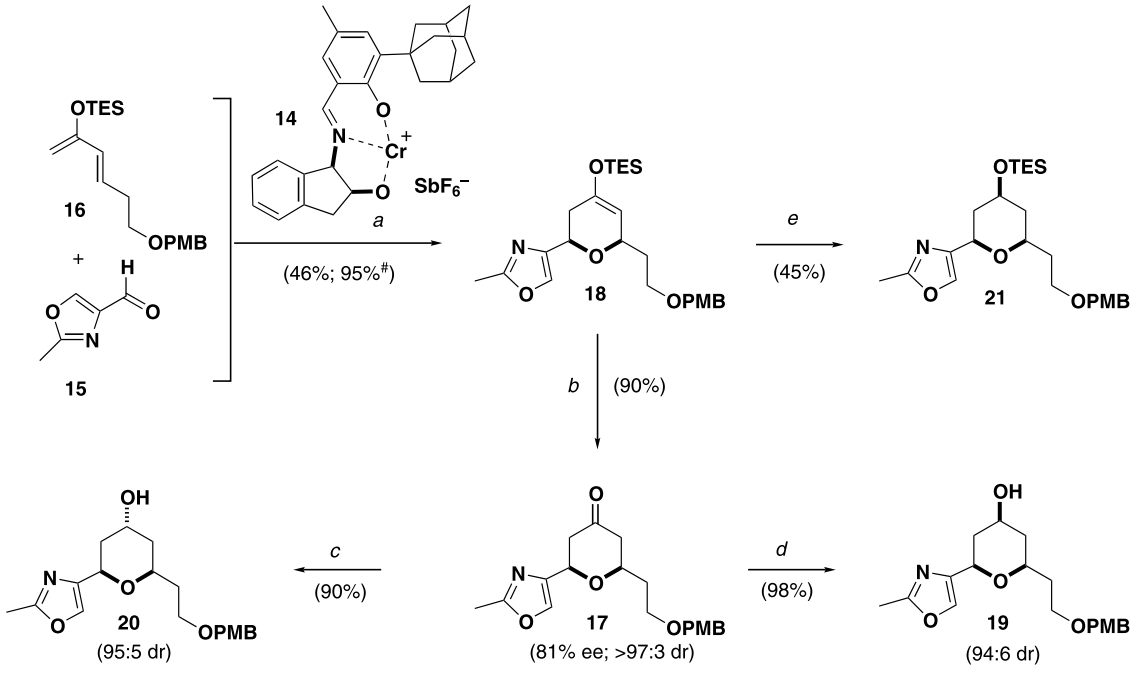
The aldehyde **9** was then elaborated into **4** by a Peterson olefination performed using oxazole **11**.[10] Thus, lithiation of **11** with $LiNEt_2$ at −78°C, followed by addition of aldehyde **9** led to efficient formation of the coupled product **12**, albeit with 2.2:1 *E*/*Z* selectivity. This mixture of geometric isomers was then completely equilibrated[5a] under mild acidic conditions (PPTS, EtOH), with concomitant removal of the two TBS ethers, to give diol **13** (87%). Finally, chemoselective oxidation[11] of the primary hydroxyl group in **13** was achieved by use of catalytic TEMPO in the presence of BAIB, followed by silylation of the remaining C_{24} alcohol to give the C_{15}–C_{32} subunit **4**.

In order to assemble the C_{11}–C_{15} tetrahydropyran ring of phorboxazole A, we sought an asymmetric HDA process that would be amenable to the direct cycloaddition of an oxazole-containing aldehyde such as **4** with a suitable 2-siloxydiene. Initially, the viability of extending Jacobsen HDA methodology[12] to such heteroaromatic aldehydes was explored in a model system (Scheme 3). By employing the Cr(III) tridentate catalyst **14** (8 mol%, dry acetone, 20°C, 38 h), the asymmetric HDA reaction of oxazole aldehyde **15** proceeded with the 2-siloxydiene **16**[2c,13] to generate the 2,6-*cis*-tetrahydropyran **17** in 81% ee and 85% yield based on

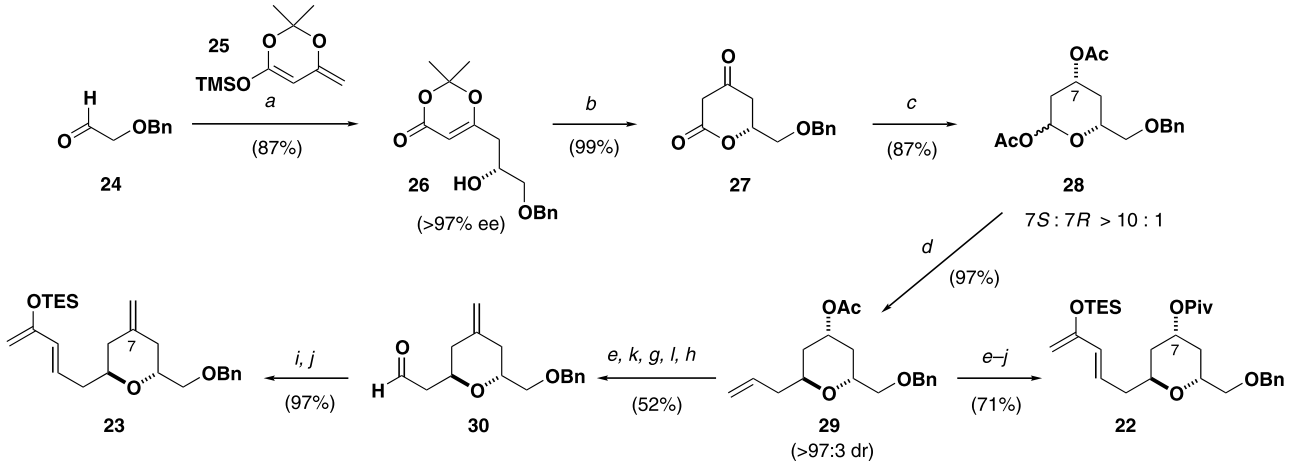


Scheme 2. *Reagents and conditions*: (*a*) **5**, ^{c}Hex$_2$BCl, Et_3N, Et_2O, 0°C, 1 h; **6**, −78 to −20°C, 18 h; H_2O_2, MeOH, pH 7 buffer; (*b*) ^{i}PrCHO, cat. SmI_2, THF, −20°C, 1.5 h; (*c*) TBSCl, ImH, DMAP, DMF, 20°C, 24 h; (*d*) DDQ, 20:1 CH_2Cl_2/pH 7 buffer, 20°C, 2 h; (*e*) $(COCl)_2$, DMSO, −78°C, 1.5 h; Et_3N, −78 to 20°C; (*f*) $(MeO)_2P(O)CH_2C(O)NMe(OMe)$, LiCl, DBU, 4:1 MeCN/$CH_2Cl_2$, 20°C, 2.5 h; (*g*) DIBAL (7 equiv.), PhMe, −78°C, 2 h; NH_4Cl, 16 h; 8:3 NH_4Cl/1N HCl (aq), 20 min; (*h*) $LiNEt_2$, THF, −78°C; (*i*) PPTS (25 equiv.), EtOH, Δ, 2 days; (*j*) TEMPO (cat.), $PhI(OAc)_2$ (1.3 equiv.), CH_2Cl_2, 20°C, 30 min; (*k*) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C.

consumed **16**, following TBAF/AcOH hydrolysis of the intermediate silyl enol ether **18**.[14] No *trans*-tetrahydropyran product was detected. By suitable choice of hydride reducing agent, the ketone **17** could then be transformed selectively into the equatorial and axial alcohols **19** and **20**, as required for phorboxazoles B and A, respectively. Alternatively, direct Pd-catalysed hydrogenation of the intermediate silyl enol ether **18** gave rise to the equatorial TES ether **21**, which could be converted into **19** by desilylation. Confirmation of the all-equatorial substitution in tetrahydropyran **19** was realised by NOE analysis, while derivatisation as the (*R*)- and (*S*)-MTPA esters enabled determination of the absolute configuration indicated, in agreement with the expected[12] sense of ligand stereoinduction. This model study demonstrated that the Jacobsen HDA reaction could indeed be used for the asymmetric assembly of the oxazole-tetrahydropyran ring system contained within the phorboxazole skeleton.



Scheme 3. *Reagents and conditions*: (*a*) **14** (8 mol%), 4 Å mol. sieves, **15**, Me_2CO, 3 h; **16**, 38 h; (*b*) AcOH (2 equiv.), TBAF (1.5 equiv.), THF, 20°C, 1.5 h; (*c*) L-Selectride, THF, −105°C, 2 h; (*d*) $NaBH_4$, MeOH, 0°C, 1 h; (*e*) 10% Pd/C (cat.), MeOH, H_2, 3 h, 20°C. # Yield based on recovered **16** and the corresponding enone hydrolysis product.

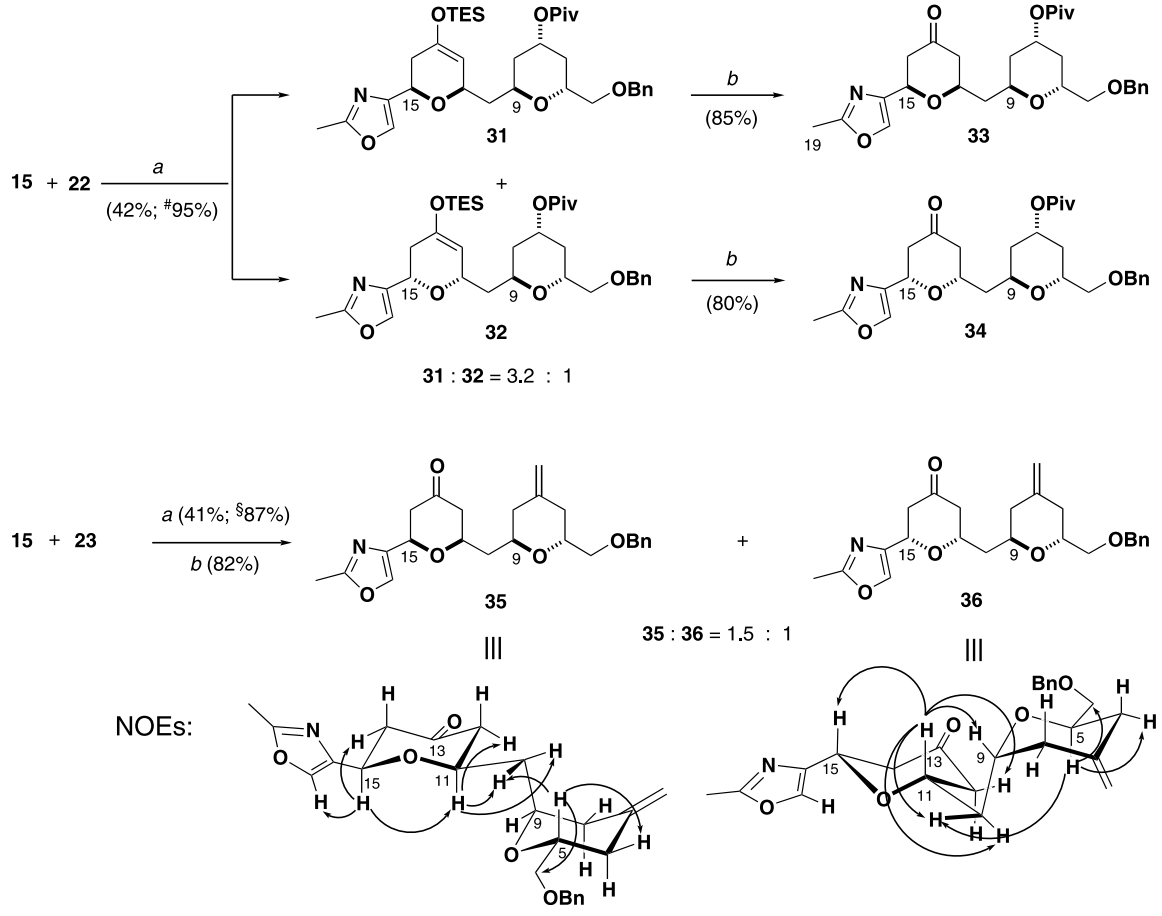


Scheme 4. *Reagents and conditions*: (*a*) [(*R*,*R*)Cu(Ph-pybox)]$(SbF_6)_2$ (5 mol%), CH_2Cl_2, −78°C, 16 h; PPTS, MeOH; (*b*) K_2CO_3, MeOH, 20°C, 17 h; (*c*) DIBAL, CH_2Cl_2, −50°C; Ac_2O, py, DMAP, CH_2Cl_2, −78 to 0°C; (*d*) $TMSCH_2CH{=}CH_2$, $BF_3{\cdot}OEt_2$, TMSOTf (0.2 equiv.), 4 Å mol. sieves, MeCN, −30 to −18°C, 1.5 h; (*e*) K_2CO_3, MeOH, 20°C, 30 min; (*f*) PivCl, py, DMAP, CH_2Cl_2, 0 to 20°C, 16 h; (*g*) OsO_4 (cat.), NMO, Me_2CO/H_2O; (*h*) $Pb(OAc)_4$, Na_2CO_3, CH_2Cl_2, 0 to 20°C, 30 min; (*i*) LiCl, DBU, $(MeO)_2P(O)CH_2COMe$, $MeCN/CH_2Cl_2$, 20°C, 3 h; (*j*) TESOTf, Et_3N, Et_2O, 0 to 20°C; (*k*) Dess–Martin periodinane, CH_2Cl_2, 20°C, 1 h; (*l*) $MePPh_3{}^+Br^-$, PhLi, 2 h, THF, 0 to 20°C, 1.5 h.

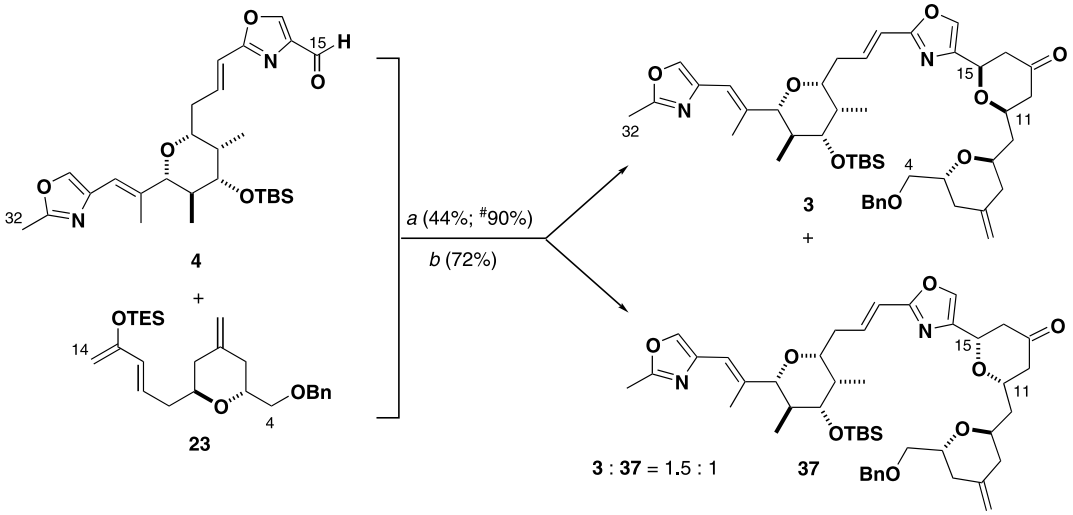
In order to examine the scope of this HDA methodology in more complex situations, the more elaborate 2-silyloxydienes **22** and **23**, containing the C_5–C_9 *trans*-tetrahydropyran ring of the phorboxazoles, were prepared as shown in Scheme 4. This sequence commenced with an enantioselective Evans aldol reaction performed between aldehyde **24** and dienolate **25** catalysed by [(*R*,*R*)Cu(Ph-pybox)](SbF$_6$)$_2$.[15] Base-mediated cyclisation of the resulting aldol adduct **26** (>97% ee) formed the keto lactone **27**, which was converted by DIBAL reduction and in situ acylation with acetic anhydride,[16] in the presence of pyridine and DMAP, into the bis-acetate **28**. Optimal selectivity for the (7*S*)-epimer **28** was obtained by performing the reduction step at −50°C. Anomeric alkylation[17] of **28** by allyltrimethylsilane proceeded cleanly to give the key intermediate **29** with high diastereoselectivity (>97:3 dr). From tetrahydropyran **29**, the 2-silyloxydiene **22** containing a pivalate substituent at C_7 was then accessed in seven steps and 71% yield, whilst diene **23** containing an *exo*-methylene was obtained in the same number of steps and 50% yield via aldehyde **30**. In both cases, the HWE homologation steps and silyl enol ether formation (TESOTf, Et_3N) from the resulting (*E*)-enones proceeded smoothly.

Having prepared the 2-silyloxydienes **22** and **23**, we initially examined their HDA reactions with the simpler oxazole aldehyde **15** (Scheme 5). In the presence of the tridentate Cr(III) catalyst **14**, the C_7–OPiv substituted diene **22** underwent HDA reaction with **15** in acetone to provide a 3.2:1 mixture of the diastereomeric *endo*-cycloadducts **31** and **32** in 42% combined yield (95% based on consumed **22**). These intermediates were hydrolysed to the corresponding ketones **33** and **34**, which were separable by chromatography. In comparison, the corresponding HDA reaction performed with the C_7-methylene substituted diene **23** proceeded with a lower level of stereocontrol, resulting in a 1.5:1 mixture of the diastereomeric *cis*-tetrahydropyrans **35** and **36** after hydrolysis, in favour of the desired adduct **35**, where these were distinguished by NOE analysis as indicated.

This same HDA coupling protocol was then examined with the more complex oxazole aldehyde **4**, which now incorporates the full C_{15}–C_{32} sequence of the phorboxazoles (Scheme 6). Using the same batch of Jacobsen catalyst **14** and the conditions employed in the formation of **35**, the HDA reaction with 2-silyloxydiene **23** provided the intermediate *endo*-cycloadducts in 44%



Scheme 5. *Reagents and conditions*: (*a*) Catalyst **14** (17 mol%), 4 Å mol. sieves, **15**, Me_2CO, 3 h; then diene **22** or **23**, 38 h; (*b*) AcOH (2 equiv.), TBAF (1.5 equiv.), THF, 20°C, 1.5 h. # Yield based on recovered **22** and the corresponding enone hydrolysis product. §Yield based on recovered **23**.



Scheme 6. *Reagents and conditions*: (*a*) Catalyst **14** (17 mol%), 4 Å mol. sieves, **4**, Me_2CO, 3 h; then diene **23**, 38 h; (*b*) AcOH (2 equiv.), TBAF (1.5 equiv.), THF, 20°C, 1.5 h. # Yield based on recovered **23**.

yield (90% based on consumed **23**) with moderate selectivity, along with recovered diene **23** and aldehyde **4**. These silyl enol ethers were hydrolysed and separated by HPLC to give the individually characterised[18] diastereomeric ketones **3** and **37**, in a ratio of 1.5:1, where the major product **3** corresponds to the full pentacyclic C_4–C_{32} segment of the phorboxazoles.

In summary, we have demonstrated that the Jacobsen HDA reaction can be applied with some success to the coupling of complex, highly functionalised substrates, in the context of a convergent approach to assembling the phorboxazole ring system. Studies are underway to address the stereochemical variability in these transformations, by further examining the influence of substrate structure and catalyst loading, in order to use this asymmetric HDA protocol as a key coupling step in the total synthesis of phorboxazole A.[19]

Acknowledgements

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14. The absolute configuration was determined by Mosher ester derivatisation of the equatorial alcohol **19**. This also enabled quantification of the enantiomeric excess, which was corroborated by chiral HPLC (Daicel AD column) analysis of **17** and comparison with *ent*-**17** made using the enantiomeric Jacobsen catalyst.
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18. All new compounds gave spectroscopic data in agreement with the structures indicated and stereochemical proof was obtained via Mosher ester and NOE analysis where applicable. Compound **3** was isolated after HPLC purification as an oil: $[\alpha]_D^{20} = +27.7$ (*c* 0.13, $CHCl_3$); IR ($CHCl_3$ solution) 2985 (w), 2957 (m), 2928 (m), 2854 (m), 1717 (s, C=O), 1660 (w), 1600 (m), 1586 (w), 1492 (w), 1467 (w), 1455 (m), 1430 (w), 1376 (m), 1362 (m), 1347 (w), 1316 (w), 1256 (m); ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.49 (1H, s, H_{30}), 7.47 (1H, s, H_{17}), 7.35–7.26 (5H, m, PhH), 6.67 (1H, ddd, $J=15.7$, 8.1, 6.6 Hz, H_{20}), 6.32 (1H, d, $J=16.0$ Hz, H_{19}), 6.18 (1H, s, H_{28}), 4.77 (1H, br s, H_{51a}), 4.74 (1H, br s, H_{51b}), 4.61 (1H, dd, $J=11.7$, 2.4 Hz, H_{15}), 4.54 (2H, ABq, $J=12.1$ Hz, $\delta_a=4.58$, $\delta_b=4.50$, PhCH_2O), 4.02 (1H, app sextet, $J=4.7$ Hz, H_9), 3.96 (1H, m, H_5), 3.92 (1H, m, H_{11}), 3.54–3.51 (2H, m, H_{4a} and H_{22}), 3.45–3.40 (3H, m, H_{4b}, H_{24} and H_{26}), 2.75 (1H, dd, $J=14.5$, 11.9 Hz, H_{14a}), 2.60–2.57 (3H, m, H_{14b}, H_{21a} and H_{12a}), 2.44 (3H, s, Me_{32}), 2.42–2.38 (2H, m, H_{12b} and H_{8a}), 2.32–2.28 (2H, m, H_{6a} and H_{21b}), 2.23 (1H, ddd, $J=14.5$, 9.2, 5.4 Hz, H_{10a}), 2.12 (1H, dd, $J=13.2$, 7.5 Hz, H_{6b}), 2.02 (1H, dd, $J=13.6$, 5.4 Hz, H_{8b}), 1.91 (3H, s, Me_{48}), 1.78 (1H, m, H_{23}), 1.73 (1H, m, H_{25}), 1.63 (1H, obsc m, H_{10b}), 0.98 (3H, d, $J=6.8$ Hz, Me_{50}), 0.91 (9H, s, $SiC(CH_3)_3$), 0.75 (3H, d, $J=6.5$ Hz, Me_{49}), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ_C 206.0, 161.5, 160.6, 141.2, 140.9, 138.2, 138.1, 137.8, 137.1, 135.5, 134.4, 128.4, 127.6, 127.5, 118.6, 118.0, 110.9, 88.8, 77.7, 77.2, 74.3, 73.3, 71.8, 71.2, 70.8, 68.9, 47.0, 46.3, 39.3, 39.2, 38.9, 36.5, 36.4, 34.8, 25.8, 18.1, 14.3, 13.9, 13.8, 5.9, −4.1, −4.8; HRMS (+ESI) calcd for $C_{46}H_{64}N_2O_8SiNa$ (MNa^+) 823.4330 found 823.4324.
19. After submission of this manuscript the Pattenden and Williams groups disclosed their completed total syntheses of phorboxazole A, see: González, M. A.; Pattenden, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 1255. Williams, D. R.; Kiryanov, A. A.; Emde, U.; Clark, M. P.; Berliner, M. A.; Reeves, J. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 1258.