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Toward the Total Synthesis of the Brasilinolides: Construction of a Differentially Protected C20−C38 Segment

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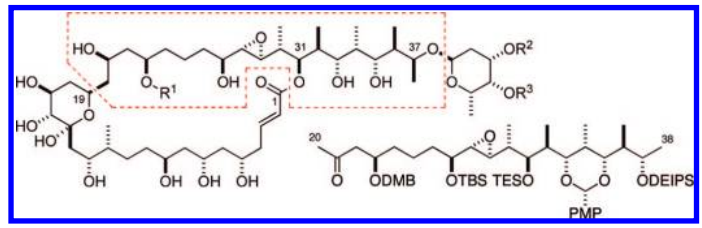
ABSTRACT



An efficient, convergent synthesis of a differentially protected C20−C38 segment of the brasilinolides is described. Iterative 1,4-*syn* aldol additions and ketone reductions were employed to construct the two related stereotetrads, while a sequence of Horner−Wadsworth−Emmons (HWE) coupling, CBS reduction, and Sharpless AE installed the epoxy alcohol functionality.

Following on from the spectacular clinical success of the cyclosporins in counteracting tissue rejection in human organ transplantation, the brasilinolides (**1a**−**c**, Scheme 1) are a recent addition to an important class of immunosuppressive macrolides that include FK506, rapamycin, and sanglifehrin.[1] First isolated in 1996 by the Mikami and Kobayashi groups from the pathogenic actinomycete *Nocardia brasiliensis* IFM-0406,[2] brasilinolide A (**1a**) exhibited immunosuppressive activity in the mouse mixed lymphocyte reaction, with an IC_{50} of 0.625 μg/mL, and showed no toxicity at 500 mg/kg. The congeneric macrolide brasilinolide B (**1b**) was reported to be active against a range of fungi and bacteria.[3] Recently, the relative and absolute configuration was determined *inter alia* by controlled chemical degradation of a third congener, brasilinolide C (**1c**), and detailed spectroscopic studies of the resulting fragments.[4]

Altogether, the pronounced biological activities of the brasilinolides, along with the low toxicity profile and favorable physicochemical properties, make their further evaluation as lead structures appealing. Following on from our recently reported synthesis of the southern C1−C19 polyol segment **2** of the brasilinolides,[5] we now describe an efficient stereocontrolled construction of the corresponding differentially protected C20−C38 northern hemisphere **3**.

As outlined in Scheme 1, access to all three congeners of the brasilinolides was planned to arise from the late-stage attachment of the appropriate C23 side chain and C37-*O*-

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(1) For a review of natural products as immunosupressive agents, see: Mann, J. *Nat. Prod. Rep.* **2001**, *18*, 417.

(2) (a) Shigemori, H.; Tanaka, Y.; Yazawa, K.; Mikami, Y.; Kobayashi, J. *Tetrahedron* **1996**, *52*, 9031. (b) Tanaka, Y.; Komaki, H.; Yazawa, K.; Mikami, Y.; Nemoto, A.; Tojyo, T.; Kadowaki, K.; Shigemori, H.; Kobayashi, J. *J. Antibiot.* **1997**, *50*, 1036.

(3) Mikami, Y.; Komaki, H.; Imai, T.; Yazawa, K.; Nemoto, A.; Tanaka, Y.; Gräfe, U. *J. Antibiot.* **2000**, *53*, 70.

(4) Komatsu, K.; Tsuda, M.; Tanaka, Y.; Mikami, Y.; Kobayashi, J. *J. Org. Chem.* **2004**, *69*, 1535.

(5) Paterson, I.; Mühlthau, F. A.; Cordier, C. J.; Housden, M. P.; Burton, P. M.; Loiseleur, O. *Org. Lett.* **2009**, *11*, 353–356.

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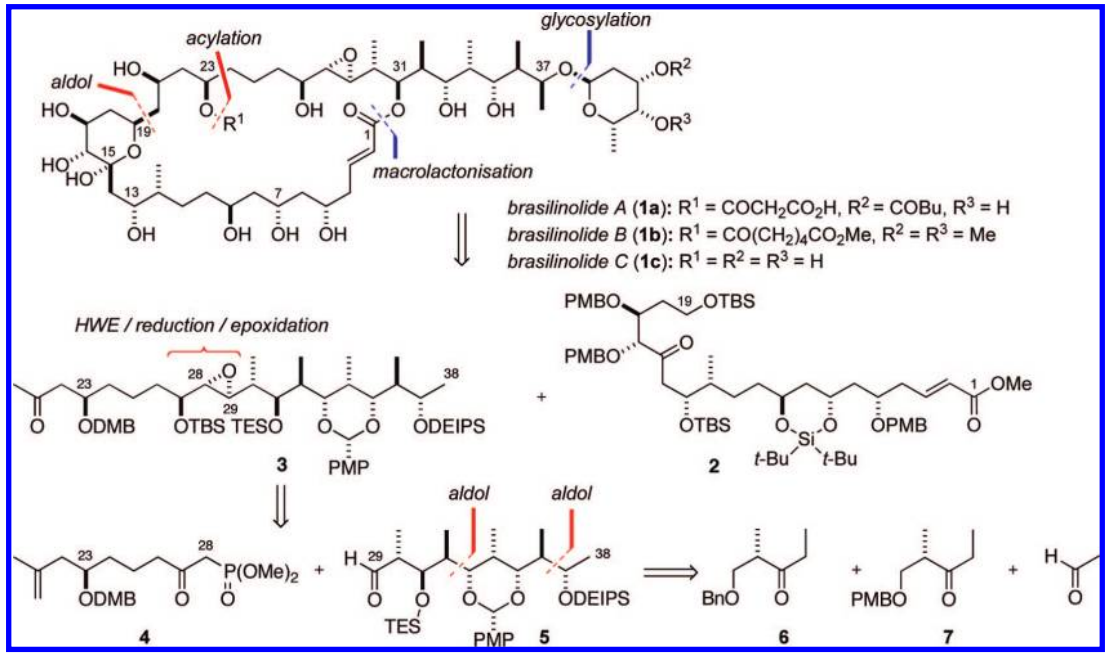
Scheme 1. Retrosynthetic Analysis of the Brasilinolides



glycosidation, following closure of the 32-membered macrolide. The northern portion of the brasilinolide structure is characterized by 11 contiguous stereocenters, together with an isolated stereocenter at C23, and requires suitable differentiation of six secondary hydroxyls in the synthetic route, as well as installation of the epoxide. A complex aldol coupling between methyl ketone **3** and a C19 aldehyde derived from **2** was proposed, followed by C21 reduction and hemiacetal formation, leading to the projected assembly of the full C1−C38 *seco*-acid precursor. Further analysis of segment **3** suggested a C28−C29 disconnection as an attractive way to handle the installation of the epoxide and the remote C23 stereocenter, leading back, in turn, to phosphonate **4** and the stereochemically elaborate aldehyde **5**. As indicated in Figure 1, detailed examination of aldehyde **5** reveals two similar stereotetrads with an epimeric relationship between C31 and C35. Thus, two iterative aldol reactions employing the (*E*)-dicyclohexylboron enolates derived from the ethyl ketones **6** and **7** (Scheme 1) were selected to configure the contiguous 1,4-*syn*-3,4-*anti* relationships *via* effective substrate-based induction.[6] Consequently, aldol-type bond scissions across C32−C33 and C36−C37 in **5** were envisaged, with the C31 and C35 hydroxyl centers to be installed *via* appropriate ketone reductions.

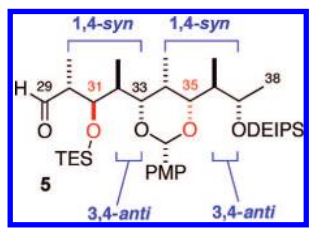
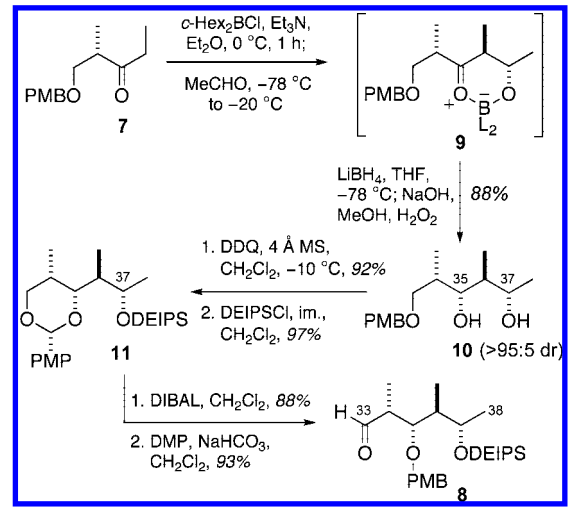


Figure 1. Stereotetrads embedded in the C29−C38 segment.

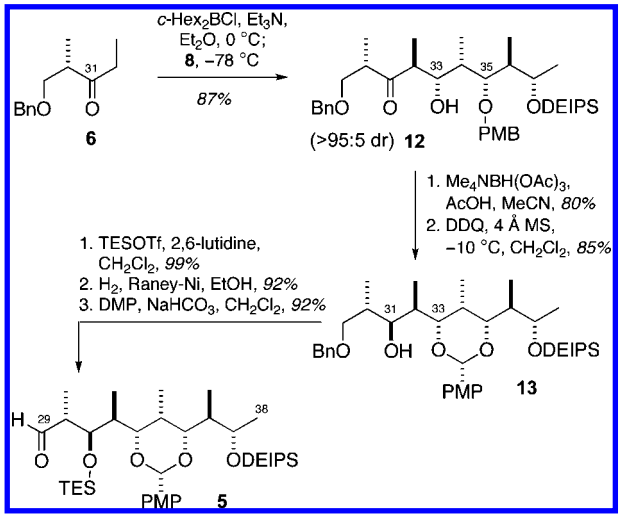
Scheme 2



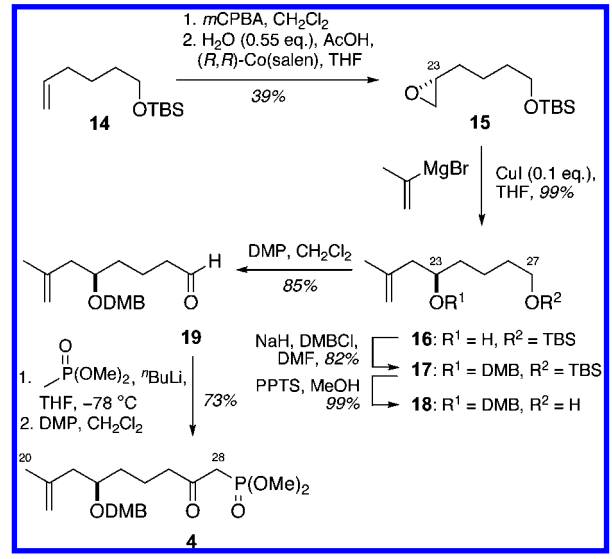
Synthesis of the initial stereotetrad associated with the C33−C38 aldehyde **8** (Scheme 2) commenced with enolization of the ethyl ketone **7**[6a] using *c*-Hex$_2$BCl/Et$_3$N. Addition

(6) (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535. (b) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (c) Paterson, I.; Ashton, K.; Britton, R.; Cecere, G.; Chouraqui, G.; Florence, G. J.; Knust, H.; Stafford, J. *Chem. Asian J.* **2008**, *3*, 367.

Scheme 3



Scheme 4



of the resulting (*E*)-enolate to acetaldehyde set the 1,4-*syn*-3,4-*anti* relationship in the intermediate aldolate **9** as expected[6] and was followed by an *in situ* ketone reduction using $LiBH_4$.[7] After oxidative cleavage of the resulting boronate ester, the 1,3-*syn* diol **10** was isolated in 88% yield and >95:5 dr, thereby efficiently controlling the configuration at the three new stereocenters. The hydroxyl groups were then differentiated[8a] by exposure of the PMB ether **10** to anhydrous DDQ oxidation conditions which afforded the corresponding six-membered PMP acetal in 92% yield. A DEIPS group[8b] was then appended to the remaining C37 hydroxyl to give the ether **11** (97%). Further elaboration to the aldehyde **8** was then effected by the regioselective reductive ring opening of the PMP acetal using DIBAL and Dess−Martin periodinane-mediated oxidation of the resulting C33 alcohol.

With aldehyde **8** in hand, attention focused on the installation of the second stereotetrad contained within the C30−C38 tetrapropionate segment of the brasilinolides (Scheme 3). Thus, an aldol addition of the (*E*)-dicyclohexylboron enolate derived from ethyl ketone **6**[6b] to aldehyde **8** was initiated at −78 °C and, with warming to −20 °C in Et_2O, afforded adduct **12** cleanly (87%, >95:5 dr). On this occasion, a 1,3-*anti* reduction[9] of the aldol adduct was required. Consequently, treatment of **12** with $Me_4NBH(OAc)_3$ gave the corresponding 1,3-*anti* diol with high diastereoselectivity. Once again, we were able to differentiate the hydroxyl groups formed in this operation by using DDQ to oxidize the PMB ether at C35 and generate the PMP acetal **13** in 85% yield.[10] The remaining strategically important alcohol at C31 was then protected as a TES ether. Care was needed to chemoselectively cleave the C29 benzyl ether in the presence of the PMP acetal. Yonemitsu and co-workers' hydrogenolysis conditions using W-2 Raney nickel proved to be optimum (92%),[11] giving the desired primary alcohol with no detectable PMP acetal cleavage. Finally, a Dess−Martin oxidation provided the required C29−C38 aldehyde **5** in 11 steps and 32% overall yield from ketone **7**. This efficient aldol-based sequence proved readily scalable and was used to produce multigram quantities of **5**.

Attention now turned to the preparation of the β-ketophosphonate **4** required as the HWE coupling partner for **5** (Scheme 4). After some experimentation, a hydrolytic kinetic resolution (HKR) approach was selected to set the configuration at C23. Thus, alkene **14** was epoxidized using *m*CPBA and then subjected to the HKR conditions developed by Jacobsen and co-workers,[12] using (*R*,*R*)-Co(salen) as the catalyst, to provide essentially enantiopure **15**. This epoxide in turn was opened by *iso*propenyl magnesium bromide in the presence of catalytic CuI to give alcohol **16** (99% ee). Next, DMB protection of **16** (NaH, DMBCl) was followed by cleavage of the TBS ether in **17** to give the alcohol **18**. Conversion of the derived aldehyde **19** into the β-ketophosphonate **4** was accomplished by addition of $LiCH_2P(O)(OMe)_2$ and subsequent Dess-Martin periodinane-mediated oxidation. This readily scalable sequence proceeded in 19% overall yield from 5-hexen-1-ol.

With both fragments **4** and **5** in hand, we could now investigate their Horner−Wadsworth−Emmons coupling (Scheme 5). A screen of HWE conditions revealed $Ba(OH)_2$ in wet THF[13] to be optimum, affording the enone **20** cleanly (91%, >95:5 *E*:*Z*). Importantly, this reaction proceeded

(7) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811.

(8) (a) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 889. (b) The selection of hydroxyl protecting groups in the C20−C38 segment **3** was made to potentially enable access to all three brasilinolide congeners by suitable derivatization at C23 and C37.

(9) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

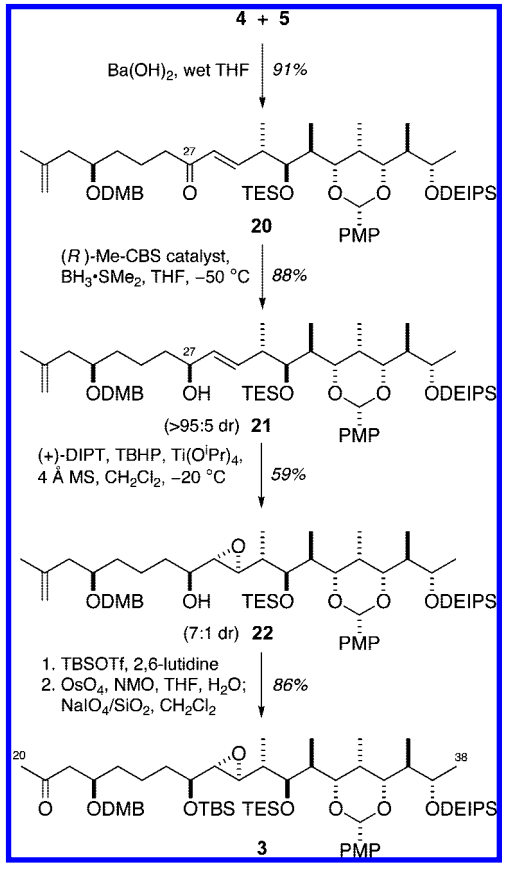
(10) The (33*R*, 34*S*, 35*R*) configurational assignments were confirmed by NOE analysis of this acetal (see the Supporting Information).

(11) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(12) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124* (7), 1307.

(13) Paterson, I.; Yeung, K-S.; Smaill, J. B. *Synlett* **1993**, 774.

Scheme 5



without any detectable elimination of the C31-OTES group from aldehyde **5**, which proved to be a persistent problem when using other bases.

A reagent-controlled reduction of enone **20** was now required. The (*R*)-Me-CBS reagent was found to give excellent selectivity in setting the desired configuration at C27, leading to the allylic alcohol **21** (88%, >95:5 dr).[14,15] The correctly configured *trans*-epoxide in **22** was then installed using Sharpless asymmetric epoxidation conditions employing (+)-DIPT/Ti(^{i}OPr)$_4$/^{t}BuOOH (59%, 7:1 dr).[16] Following TBS protection of the C27 hydroxyl in **22**, the required ketone at C21 was introduced *via* OsO_4-mediated dihydroxylation of the alkene and cleavage of the resulting diol with $NaIO_4/SiO_2$[17] to afford **3** (86%), corresponding to the targeted C20−C38 segment of the brasilinolides.

In summary, we have developed a highly stereocontrolled synthesis of a differentially protected C20−C38 segment **3** of the brasilinolides that proceeds in 16 steps and 13% overall yield in the longest linear sequence from the ethyl ketone (*S*)-**7**.[18] Studies into the complex aldol coupling of methyl ketone **3** with a suitable C19 aldehyde derived from **2**[5] (Scheme 1), together with further efforts toward completion of the total synthesis of the brasilinolide macrolides, are ongoing.

Acknowledgment. We thank the EPSRC (EP/F025734/1) and Syngenta for support and the Deutsche Akademie der Naturforser Leopoldina (F.A.M.; BMBF-LPD 9901/8-148) and the Herchel Smith Postdoctoral Fellowships Fund at Cambridge (C.J.C.) for additional funding.

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

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(14) The (27*S*)-configuration was confirmed by Mosher ester analysis using the Kakisawa method (see the Supporting Information). Ohtani, I.; Kasumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(15) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(16) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers: New York, 1993; p 103.

(17) Zhong, Y.-L.; Shing, T. K. M. *J. Org. Chem.* **1997**, *62*, 2622.

(18) This is prepared in three steps and 77% yield from methyl (*S*)-2-methyl-3-hydroxypropionate (see ref 6a).