

Toward the Total Synthesis of the Brasilinolides: Stereocontrolled Assembly of a C1–C19 Polyol Segment

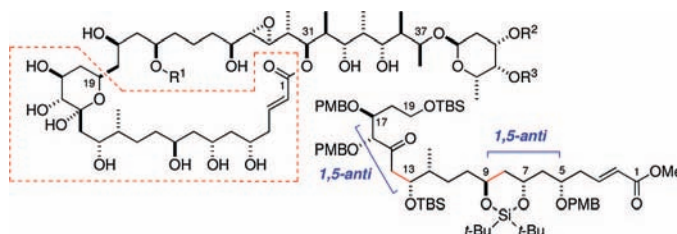
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ABSTRACT



Two highly convergent syntheses of a fully protected C1–C19 polyol subunit of the brasilinolide family of immunosuppressive macrolides are described, exploiting boron-mediated 1,5-*anti* aldol couplings to form the C8–C9 and C13–C14 bonds.

The brasilinolides (**1a–c**, Scheme 1), first isolated in 1996 by Kobayashi and co-workers from the pathogenic actinomycete *Nocardia brasiliensis* IFM-0406, constitute a structurally unique family of bioactive 32-membered macrolides.¹ Recently, the relative and absolute configuration was determined inter alia by controlled chemical degradation of brasilinolide C (**1c**) and detailed spectroscopic studies of the resulting fragments.²

Brasilinolide A (**1a**) exhibits immunosuppressive activity in the mouse mixed lymphocyte reaction, with an IC₅₀ of 0.625 $\mu\text{g mL}^{-1}$, and represents a recent addition to an important class of macrolactone immunosuppressants.³ While

the immunosuppressive effect is somewhat lower compared to cyclosporin A, rapamycin, and FK506, brasilinolide A stands out in showing no acute toxicity, even up to 500 mg kg⁻¹. In addition, brasilinolide A is reported to show significant antifungal activity, and brasilinolide B (**1b**) is active against a range of fungi and bacteria. Altogether, their pronounced biological activities, along with the low toxicity profile and favorable physicochemical properties, support further evaluation of the brasilinolides. As part of studies toward a projected total synthesis of these highly oxygenated macrolides, we now report an expedient aldol-based construction of the fully protected C1–C19 polyol segment **2**, corresponding to the southern hemisphere region of the brasilinolides.

As outlined retrosynthetically in Scheme 1, simplification of brasilinolide A (**1a**) is achieved by the late-stage attachment of the polar C23-*O*-malonyl substituent and C37-*O*-glycosylation, following macrolactonization. An aldol coupling of methyl ketone fragment **3** with a suitable aldehyde derived from **2** is envisaged to control the C19 stereocenter and trigger hemiacetal formation with the C15 ketone,

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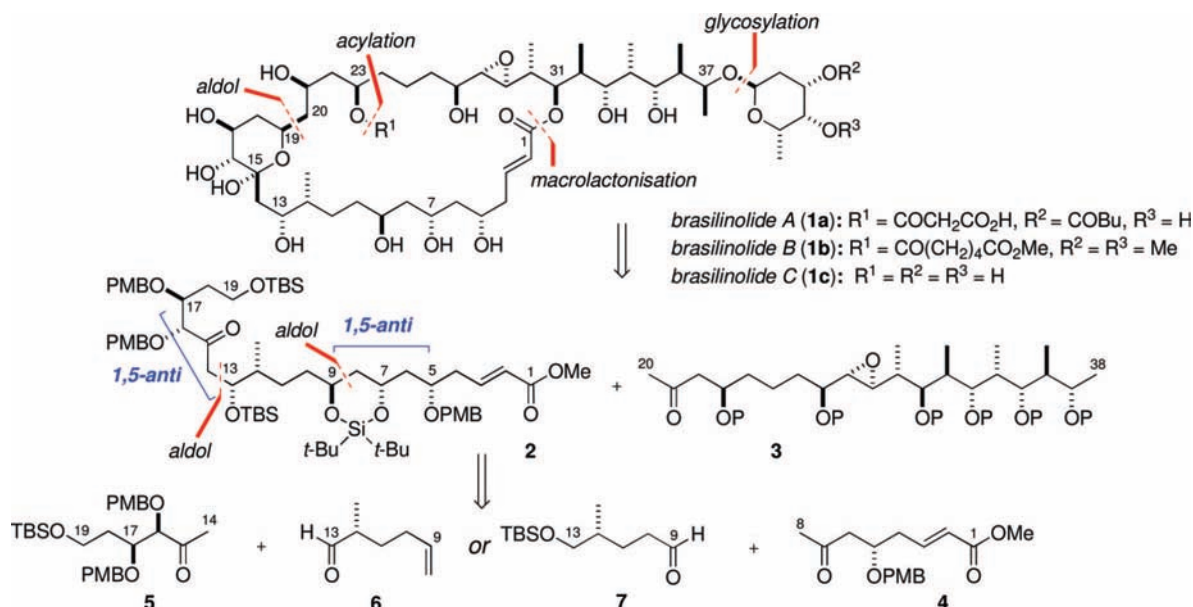
[‡] Syngenta.

(1) (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.; Tojo, T.; Kadowaki, K.; Shigemori, H.; Kobayashi, J. *J. Antibiot.* **1997**, 50, 1036. (c) Mikami, Y.; Komaki, H.; Imai, T.; Yazawa, K.; Nemoto, A.; Tanaka, Y.; Gräfe, U. *J. Antibiot.* **2000**, 53, 70.

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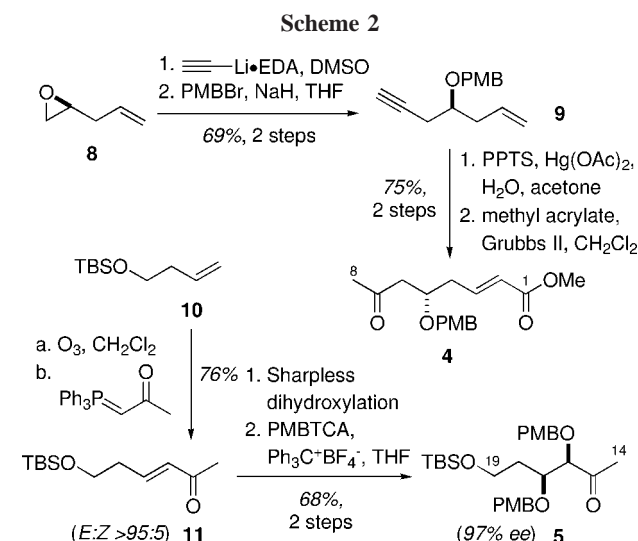
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Scheme 1. Retrosynthetic Analysis of the Brasilinolides



leading to the full C1–C38 *seco*-acid precursor. Further analysis of the pivotal C1–C19 segment **2** suggests that aldol-type bond scissions might be made productively at C8–C9 and C13–C14. This highly convergent strategy relies on exploiting the two 1,5-*anti* diol relationships highlighted in segment **2** using our boron aldol methodology.^{4,5} Thus, the C9 center in **2** will be configured using the C5 center by the addition of a boron enolate derived from β -alkoxy ketone **4** to a suitable aldehyde, while C13 might be set in a similar manner, exploiting the anticipated 1,5-*anti* stereoiduction from C17 in methyl ketone **5**. Given the protecting group requirements for 1,5-*anti* aldol reactions, the methyl ketones **4** and **5** have PMB ethers at C5 and C17, with aldehydes **6** and **7** selected as two possible connecting building blocks. In the two syntheses of the C1–C19 segment **2** described herein, aldehydes **6** and **7** play the role of a bifunctional C9–C13 central unit.

Synthesis of the C1–C8 ketone **4** commenced with the epoxide **8** (Scheme 2), prepared in two steps from (*S*)-(+)-epichlorohydrin.⁶ Epoxide opening proceeded at ambient temperature in DMSO using lithium acetylide ethylene diamine complex. The resulting alcohol was transformed into the PMB ether **9**, and hydration of the alkyne proceeded smoothly using PPTS (1.5 equiv) and $\text{Hg}(\text{OAc})_2$ (0.3 equiv) in wet acetone.⁷ Olefin cross-metathesis with methyl acrylate



(Grubbs II, 1 mol %)⁸ then afforded the enantiopure ketone **4** in four steps and 52% yield from **8**.

Synthesis of the C14–C19 ketone **5** (Scheme 2) relied on Sharpless asymmetric dihydroxylation and began with the silyl ether **10**, which was converted directly into the enone **11** using a method described by Hon (76%, >95:5 *E/Z*).⁹ An optimized Sharpless dihydroxylation of **11**, utilizing the $(\text{DHQ})_2\text{AQN}$ ligand, provided the required α,β -dihydroxy ketone efficiently (84%, 97% ee).^{10,11} Conversion into the bis-PMB ether (PMBTCA, cat. Ph_3CBF_4)¹² then gave the methyl ketone **5** in three steps and 49% overall yield from the silyl ether **10**.

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The reaction scheme illustrates the synthesis of compounds **6** and **7** from starting materials **12** and **14**.

Left Pathway (Starting from 12):

- Starting material **12** (a chiral amide with a phenyl group and a hydroxyl group) reacts with:
 - a. LDA, LiCl, THF, -78°C
 - b. 1-penten-3-yl iodideto yield intermediate **13** in 98% yield.
- Intermediate **13** is then converted to compound **6** (an aldehyde with a terminal alkene) in 88% yield over 2 steps, using:
 - 1. LDA, $\text{NH}_3 \cdot \text{BH}_3$
 - 2. Swern oxidationCompound **6** is obtained in 97% ee.

Right Pathway (Starting from 14):

- Starting material **14** (a chiral amide with a benzyl group and a cyclic carbamate) reacts with:
 - a. $\text{TiCl}_3(\text{O}-i\text{-Pr})$, $i\text{-Pr}_2\text{NEt}$, CH_2Cl_2
 - b. acrylonitrileto yield intermediate **15** (a nitrile) in 83% yield. Intermediate **15** is noted as a 96:4 dr.
- Intermediate **15** is then converted to compound **7** (an aldehyde with a TBSO group and a terminal alkene) in 58% yield over 3 steps, using:
 - 1. NaBH_4 , H_2O , THF
 - 2. TBSCl, imid., CH_2Cl_2
 - 3. DIBAL-H, CH_2Cl_2Compound **7** is obtained in 92% ee.

With all four building blocks **4–7** prepared, their boron-mediated aldol coupling was explored, relying on 1,5-*anti* induction from the C5 and C17 stereocenters. In the initial route examined (Scheme 4), the C8–C9 bond was formed before the C13–C14 bond. Based on our standard protocol,⁴ the methyl ketone **4** was enolized using *c*-Hex₂BCl and Et₃N at 0 °C. Addition of aldehyde **7** at –78 °C then gave the desired 1,5-*anti* adduct **16** in 88% yield and with >95:5 dr.

(11) See the Supporting Information for details.
 (12) (a) Ireland, R. E.; Liu, J.; Roper, T. D. *Tetrahedron* **1997**, *53*, 13221.
 (b) Paterson, I.; Coster, M. J.; Chen, D.Y.-K.; Acena, J. L.; Bach, J.; Keown, L.; Trieselmann, T. *Org. Biomol. Chem.* **2005**, *3*, 2420.

(14) (a) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750. (b) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

The reaction scheme illustrates the synthesis of 1,5-dicarbonyl compounds 16 and 19, and the proposed transition state for the 1,5-anti selectivity.

Synthesis of 16: Compound 4 reacts with *c*-Hex₂BCl, Et₃N, 0 °C, Et₂O, followed by 7, -78 °C → -23 °C, to yield 16 in 88% yield. Compound 16 is a 1,5-dicarbonyl compound with a 1,5-anti relationship between the carbonyl groups, indicated by a blue bracket and the label "1,5-anti".

Synthesis of 19: Compound 16 is converted to 19 in 75% yield over 2 steps using 1. CSA, MeOH and 2. DMP, NaHCO₃, CH₂Cl₂.

Synthesis of 17 and 18: Compound 16 is converted to 17 (R = H) in 95% yield using Me₄NB(OAc)₃, AcOH, MeCN. Compound 17 is then converted to 18 (R = R = Si(*t*-Bu)₂) in 70% yield using *t*-Bu₂Si(OTf)₂, lutidine, CH₂Cl₂.

Synthesis of 20: Compound 19 is converted to 20 in 70% yield using *c*-Hex₂BCl, NEt₃, 0 °C, Et₂O.

Synthesis of 22: Compound 20 is converted to 22 in 64% yield using *i*-PrCHO. Compound 22 is a 1,5-dicarbonyl compound with a 1,5-anti relationship between the carbonyl groups, indicated by a blue bracket and the label "1,5-anti".

Synthesis of 23 and 2: Compound 20 is converted to 23 (R = H) in 67% yield using TBSOTf, lutidine. Compound 23 is then converted to 2 (R = TBS) using TBSOTf, lutidine.

Proposed Transition State (TS-I): The transition state for the 1,5-anti selectivity is shown as a chair-like structure. The boron atom (B) is coordinated to the carbonyl oxygen of the aldehyde (R¹) and the carbonyl oxygen of the ketone (R²). The boron atom is also coordinated to the carbonyl oxygen of the aldehyde (R¹) and the carbonyl oxygen of the ketone (R²). The transition state is labeled "TS-I" and shows the 1,5-anti relationship between the carbonyl groups.

The pivotal aldol coupling between **5** and **19** now depended on the extension of 1,5-*anti* boron aldol methodology to include enolates such as **20** that have an alkoxy stereocenter at the α -position as well as the β -position. DFT calculations predicted that these aldol reactions will proceed preferentially through *TS-I*, where π -facial discrimination

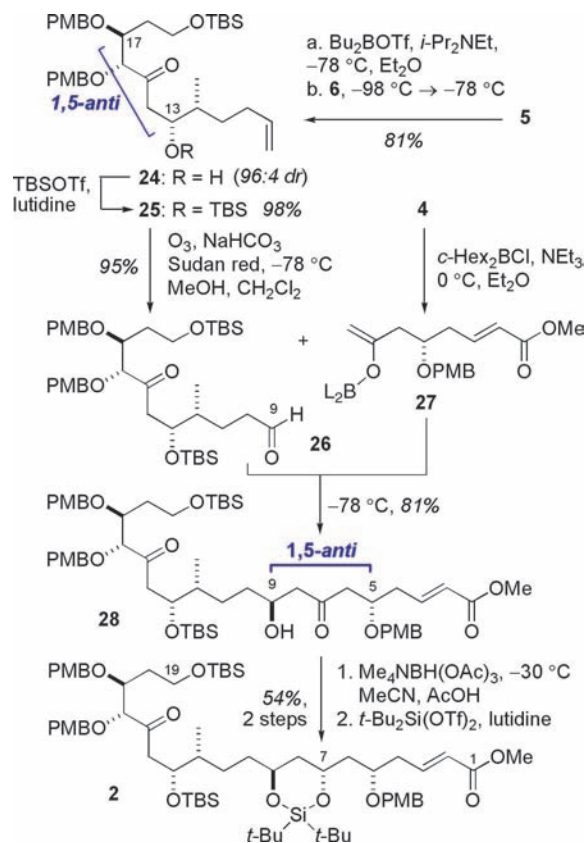
(16) The configurations of the stereocenters at C7 and C9 were confirmed by (i) conversion of **17** into the 7,9-*anti* acetonide and ^{13}C NMR analysis using Rychnovsky's method and (ii) treatment of **17** with DDQ to generate the corresponding 5,7-*syn* PMP acetal and NOE analysis. Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

to favor adduct **21** is controlled by a stabilizing formyl H-bond involving only the PMB ether oxygen at the β -center and minimization of steric interactions.¹⁷ Initially, the inherent diastereoselectivity of the boron enolate **20** derived from ketone **5** was determined by its addition to isobutyraldehyde, leading to formation of the 1,5-*anti* adduct **22** with 89:11 dr.¹⁸ Having established that the expected stereoinduction was operating, the C13–C14 aldol coupling between enolate **20** and aldehyde **19** was performed to give the required adduct **23** selectively (70%, 87:13 dr). Silylation of alcohol **23** then afforded the C1–C19 segment **2** with a longest linear sequence of 11 steps from **8** and 11.5% overall yield.

In an alternative assembly of the southern hemisphere region of the brasilinolides, the C13–C14 aldol coupling step was performed first (Scheme 5). Under optimized conditions, the methyl ketone **5** was enolized using Bu₂BOTf and *i*-Pr₂NEt at –78 °C. Addition of aldehyde **6** at –98 °C provided the desired 1,5-*anti* adduct **24** with excellent diastereoselectivity (81%, 96:4 dr). Following TBS ether formation to give **25**, the C9 aldehyde was unmasked by controlled ozonolysis¹⁹ to give **26** (95%). A C8–C9 aldol coupling was then performed with the boron enolate **27** derived from **4** using the previously developed conditions, giving the 1,5-*anti* adduct **28** with equally high diastereoselectivity (81%, >95:5 dr). The sequence was concluded with an Evans–Saksena reduction of **28** to install the C7 stereocenter, followed by protection of the resulting 1,3-*anti* diol to give **2**.²⁰ This second route to the C1–C19 segment **2** has nine steps in the longest linear sequence starting from **10** and proceeded in an improved overall yield of 17.4%.

In summary, we have completed the stereocontrolled synthesis of the fully protected C1–C19 polyol segment **2** of the brasilinolides using two highly convergent routes. Efficient fragment couplings were achieved using boron-mediated 1,5-*anti* aldol reactions. Ongoing work into the assembly of the northern hemisphere **3** (Scheme 1) should

Scheme 5



further advance the total synthesis of this novel family of immunosuppressive macrolides.

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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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(17) We thank Dr. Rob Paton for carrying out transition state calculations for R¹ = Me and R² = (*E*)-CH=CHMe, where *TS-I* leading to adduct **21** was preferred. Paton, R. S.; Goodman, J. M. *J. Org. Chem.* **2008**, *73*, 1253.

(18) The configuration was determined by use of the advanced Mosher method: Ohtani, I.; Kasumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.

(19) The use of an indicator (Sudan red 7B) was crucial to prevent oxidation of the PMB ethers. Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

(20) The spectroscopic data of **2** matched that of material prepared via the route described in Scheme 4.