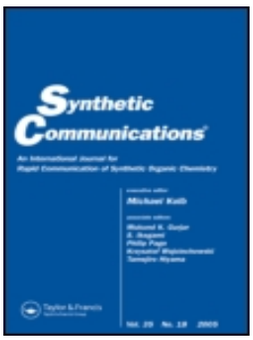

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STUDIES TOWARD THE STEREOSELECTIVE SYNTHESIS OF C13 TO C21 FRAGMENT OF THE BRASILINOLIDES FAMILY OF IMMUNOSUPPRESSIVE MACROLIDES

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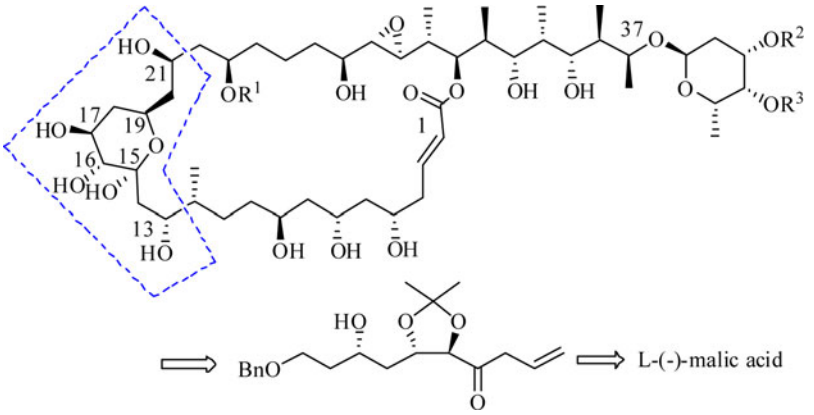
GRAPHICAL ABSTRACT



Abstract *The work describes our attempts to synthesize the C13 to C21 fragment of brasilinolides, a 32-membered macrolide class of molecule. The C13 to C21 segment encompasses six asymmetric centers and a pyran ketal moiety. The synthesis starts from L-malic acid, and the salient features of our asymmetric synthesis are opening of epoxide, assymmetric dihydroxylation for the creation of* vic*-diol, and Barbier allylation.*

Keywords Asymmetric dihydroxylation; Barbier allylation; α/β-unsaturated ketone; *vic*-diol

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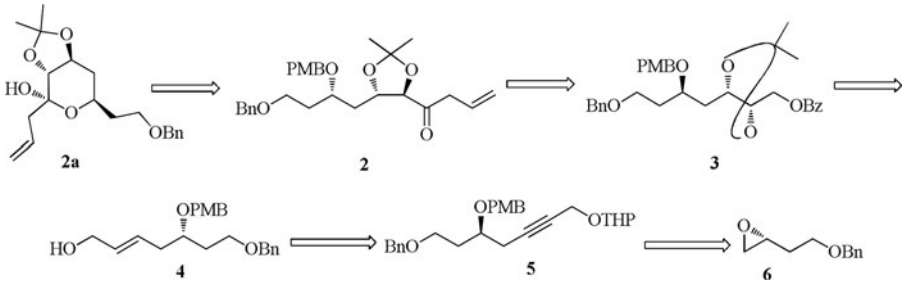


Scheme 1. Retro synthetic analysis of C13 to C21 fragment.

INTRODUCTION

The brasilinolides (**1a–c**, Scheme 1) belong to an important class of immunosuppressive agents.[1] Macrolides **1a–1c** were first isolated in 1996 from the pathogenic actinomycete *Nocardia brasiliensis* IFM-0406. They constitute a structurally unique family of bioactive 32-membered macrolides.[2] The relative and absolute configurations of **1a–1c** were determined inter alia by controlled chemical degradation of **1c** and detailed spectroscopic studies of the resulting fragments.[3] Brasilinolide A **1a** exhibits immunosuppressive activity[4] in the mouse mixed lymphocyte reaction with an IC_{50} of $0.625\,\mu g\,mL^{-1}$ and shows no acute toxicity, even up to $500\,mg\,kg^{-1}$. In addition, **1a** is reported to show significant antifungal activity, while **1b** is active against a range of fungi and bacteria. Paterson et al.[5,6] in 2009 reported highly convergent syntheses of a fully protected C1-C19 subunit and differentially protected C20-C38 segment of **1a–1c**. In continuation of our studies on the synthesis of macrolides,[7] herein, we report our studies towards the stereoselective synthesis of C13–C21 segment of **1a–1c** by asymmetric approach from L-malic acid.

RESULTS AND DISCUSSION

From the antithetic analysis of **1a–1c** (Scheme 1), the synthesis of C13–C21 fragment **2a** containing a pyran ketol was envisioned from the corresponding ketone **2**, which in turn can be obtained from benzoate **3**. Acetonide **3** in turn could be prepared from the allylic alcohol **4**, which can be made from the epoxide **6**, through **5**.

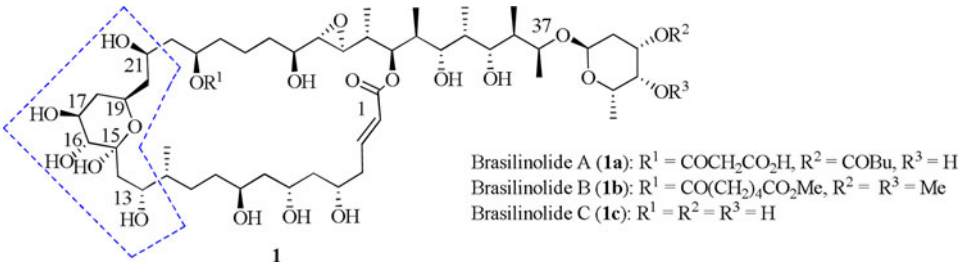
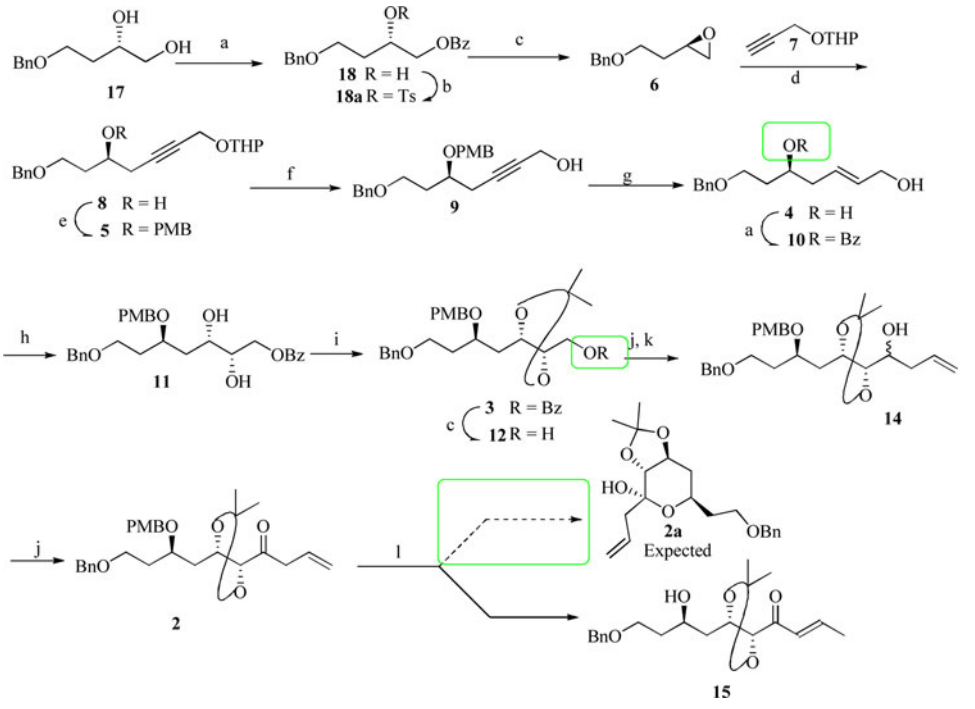


Figure 1. Structure of immunosuppressive brasilinolides.



Scheme 2. Reagents and conditions: a) BzCl, CH_2Cl_2, TEA, 0 °C-rt, 4 h; b) *p*-TsCl, CH_2Cl_2, Et_3, 0 °C-rt, 4 h; c) K_2CO_3, MeOH, 0 °C-rt, 4 h; d) *n*BuLi, BF_3OEt_2, THF, –78 °C, 1 h; e) PMB-Br, NaH, THF, 0 °C-rt, 1 h; f) PPTS, MeOH, 0 °C-rt, 1 h; g) LAH, THF, 0 °C-rt, 4 h; h) AD-mix-*α*, $MeSOzNH_2$, ^tBuOH:H_2O(l:l), 0 °C, 18 h; i) PTSA, 2,2 DMP, CH_2Cl_2, 0 °C-rt, 4 h; j) Dess-Martin Periodinane, CH_2Cl_2, 0 °C-rt, 2 h; k) Zn, allylbromide, THF, 0 °C-rt, 6 h; 1) DDQ, CH_2Cl_2: H_2O(9:l), 0 °C-rt, 1 h.

Thus, the epoxide is prepared from L-malic acid, while, the *vic*-diol at C16/C17 is proposed through asymmetric dihydroxylation.

The selective protection of known diol **17**[8] with benzoyl chloride in the presence of Et_3N and Bu_2SnO[9] in CH_2Cl_2 furnished the benzoate **18** in 75% yield. Treatment of ester **18** with *p*-TsCl, Et_3N, and dimethylaminopyridine (DMAP, cat.) in CH_2Cl_2 furnished **18a**, which on reaction with K_2CO_3 in methanol gave epoxide **6** in 76% yield. Epoxide **6** on reaction with **7** in the presence of *n*-BuLi and $BF_3 \cdot Et_2O$ in tetrahydrofuran (THF) gave alcohol **8** in 73% yield. Reaction of **8** with NaH and p-methoxybenzyl (PMB)-Br in dry THF afforded the PMB ether **5** (79%), which on *p*-toluenesulfonic acid (PTSA)–catalyzed removal of tetrahydropyranyl (THP) in methanol furnished alcohol **9** in 89% yield. Reduction of **9** with lithium aluminum hydride (LAH) in dry THF afforded the allylic alcohol **4** (77%), which on treatment with BzCl and Et_3N in CH_2Cl_2 gave bezoate **10** in 76% yield. The asymmetric dihydroxylation of benzoate **10** with AD-mix-α in the presence of methanesulfonamide in $^tBuOH/H_2O$ (1:1) afforded the diol **11** (52%), which on treatment with 2,2-dimethoxy propane in the presence of PTSA (cat.) in CH_2Cl_2 furnished the acetonide **3** in 84% yield. Further, benzoate **3** on reaction with K_2CO_3 in MeOH underwent hydrolysis to furnish the alcohol **12** (75%), which on oxidation with Dess–Martin periodinane in anhydrous CH_2Cl_2 gave the aldehyde **13**.

Zinc-mediated Barbier allylation of **13** gave allylic alcohols **14** as an inseparable mixture (80%), which on oxidation with Dess–Martin periodinane in anhydrous CH_2Cl_2 gave the ketone **2** in 75% yield. Attempted removal of the PMB group in **2** oxidatively with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[10] in aqueous CH_2Cl_2 gave an unexpected α/β-unsaturated ketone **15** in 63% yield. Further attempts to deprotect the PMB group in **2** with other reagents such as TMSCl, anisole, $SnCl_2$ (cat.)[11] in CH_2Cl_2, and ceric ammonium nitrate (CAN)[12] in CH_2Cl_2/H_2O) did not give the desired product **2a**. Several attempts for the conversion of **2** to form the expected ketol **2a** met with failure.

EXPERIMENTAL

1-((4R,5R)-5-((R)-3-(Benzyloxy)-1-(4-methoxybenzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-one (2)

To a stirred solution of diastereomeric mixture of alcohol **14** (2.1 g, 4.4 mmol) in anhydrous CH_2Cl_2 (1.5 mL) under N_2 atmosphere at 0 °C, Dess–Martin periodinane (2.2 g, 5.3 mmol) and $NaHCO_3$ (0.56 g, 6.7 mmol) were added and stirred at room temperature for 2 h. Workup as described for **13** and purification of the residue by column chromatography (silica gel, 60–120 mesh, EtOAc/hexane, 1:9) furnished **2** (1.5 g, 75%) colorless thick syrup. $[\alpha]_D^{25} = 70.03$ (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): 3068, 2923, 1720, 1661, 1513, 1455, 1377, 1302, 1242, 1213, 1093, 915, 878, 849, 820, 735, 699, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 295 K): δ 7.21 (m, 7H, Ar-H), 6.81 (d, 2H, $J = 8.5$ Hz, Ar-H), 5.75 (m, 1H, olefinic), 5.0–5.1 (m, 2H, olefinic), 4.35–4.48 (m, 4H, $2 \times ArCH_2$), 4.0 (m, 1H, OCH), 3.15–3.81 (m, 4H, OMe, OCH), 3.05–3.18 (m, 3H, $3 \times OCH$), 2.91 (m, 2H, CH_2), 1.75–1.98 (m, 2H, $2 \times CH$), 1.55–1.74 (m, 2H, $2 \times CH$), 1.35 (s, 3H, CH_3), 1.40 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8, 159.1, 138.3, 134.3, 130.6, 129.5 (2C),128.3 (2C), 127.6 (3C), 118.1, 113.7 (2C), 108.3, 83.09, 75.6, 74.0, 73.0, 71.5, 66.7, 55.2, 39.8, 37.8, 35.0, 27.3 (2C). HRMS (ESI): *m/z* calculated for $C_{28}H_{37}O_6[M+H]^+$: 470.1256; found: 470.1254.

(E)-1-((4R,5R)-5-((R)-3-(Benzyloxy)-1-hydroxypropyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-3-en-2-one (15)

To a solution of **2** (1.5 g, 3.2 mmol) in CH_2Cl_2/H_2O (10 mL; 19:1), DDQ (0.8 g, 3.8 mmol) was added and stirred at room temperature 1 h. The reation mixture was quenched with saturated $NaHCO_3$ solution (10 mL), filtered, and washed with CH_2Cl_2(20 mL). The filtrate was washed with water (15 mL), brine (10 mL), and dried (Na_2SO_4). Solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc:*n*–hexane, 1:9) to furnish **15** (0.7 g, 63%) colorless liquid. $[\alpha]_D^{25} = 58.6$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): 3018, 2935, 2872, 1714, 1623, 1513, 1452, 1379, 1315, 1275, 1214, 1164, 1091, 1027, 972, 927, 840, 840, 744, 666, 626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H, Ar-H), 7.08 (m, 1H, olefinic), 6.65 (m, 1H, olefinic), 4.51 (s, 2H, $PhCH_2$), 4.29 (m, 1H, OCH), 4.18 (m, 1H, OCH), 4.04 (m, 2H, $2 \times OCH$), 3.74–3.62 (m, 3H, OCH, $COCH_2$), 3.30 (brs, 1H, OH), 1.96–1.87 (m, 2H, CH_2),

1.84–1.76 (m, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.43 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 145.7, 133.8, 128.2 (2C), 127.5 (2C), 126.2 (2C), 110.0, 84.0, 75.6, 73.1, 68.4, 67.5, 40.7, 36.8, 27.0, 25.9, 18.4. HRMS (ESI): m/z calculated for $C_{20}H_{29}O_5[M+H]^+$: 349.2009; found: 349.2013.

CONCLUSION

In summary, the present study reports our attempts on the stereoselective synthesis of the C13–C21 segment starting from L-(–)-malic acid. The synthetic strategy involved opening of epoxide to obtain C19 stereocenter, assymmetric dihydroxylation to obtain C16/C17 *vic*-diol moiety, and Barbier allylation on aldehyde for C-C bond formation. The attempted pyran ring formation by the removal of the PMB group led to the identification of an unexpected α/β-unsaturated ketone **15** exclusively.

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SUPPLEMENTAL MATERIAL

Full experimental details, spectral data, and ^1H NMR and ^{13}C NMR of all the new products for this article can be accessed on the publisher's website.

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