Alkyne-Assisted Approach to the Formal Synthesis of Antibiotic Macrolide (–)-A26771B

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Abstract: A stereoselective formal synthesis of a 16-membered antibiotic macrolide (–)-A26771B is described starting from (*R*)-propylene oxide and (+)-diethyl tartrate. Key steps involved in this alkyne-assisted convergent approach are alkyne zipper reaction, Cadiot–Chodkiewicz coupling, and Yamaguchi macrolactonization.

Key words: alkyne, macrolide, zipper reaction, Cadiot–Chodkiewicz reaction, Yamaguchi macrolactonization

(–)-A26771B (**1**, Figure 1) is a 16-membered macrocyclic lactone, which was isolated from *Pencillium turbatum* in 1977.[1] This macrolide was found to be moderately active against Gram-positive bacteria, mycoplasma, and fungi. Structurally it possesses a γ-oxo-δ-acyloxy-α,β-unsaturated carboxyl functionality and two asymmetric centers. The interesting structural features as well as biological activity of (–)- A26771B have made it as an attractive target to the synthetic community, and various strategies have been developed either in enantiomeric or in racemic approach.[2] Our interest in alkyne-based chemistry towards synthesis of macrolides[3] prompted us to attempt the synthesis of (–)-A26771B. Described herein is a different approach to the formal synthesis of (–)-A26771B, featuring a zipper reaction, and Cadiot–Chodkiewicz coupling followed by Yamaguchi macrocyclization as the key steps. This alkyne-based convergent route is envisaged to link the two fragments **4** and **5** at C7–C8 bond towards **3**, which can be transformed into **2** via Yamaguchi macrolactonization (Scheme 1).

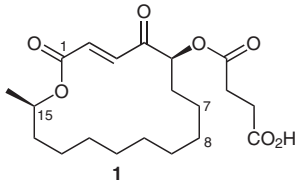

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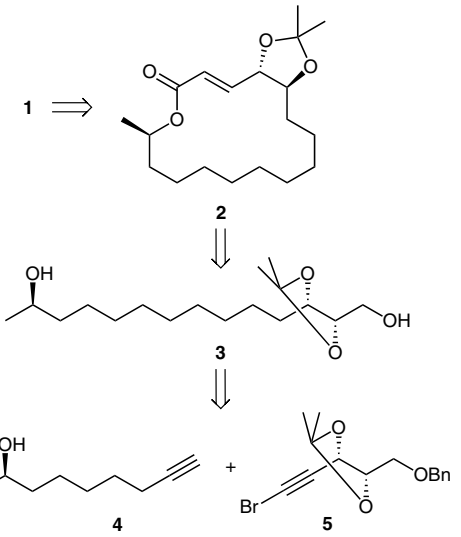
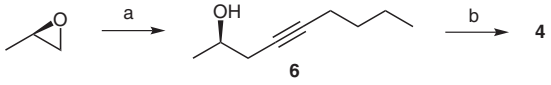
Figure 1 Structure of (–)-A26771B (**1**)

As shown in Scheme 2, alkynol **4** was obtained from (*R*)-propylene oxide, which was subjected to epoxide-opening reaction with 1-hexyne and *n*-BuLi–HMPA in THF to provide alcohol **6** in 84% yield. The internal alkyne functionality in **6** was shifted to the terminal position by the treatment of **6** under alkyne zipper reaction conditions (KH, 1,3-diamino propane) to obtain compound **4** in 81% yield.[4]



Scheme 1 Retrosynthetic analysis of **1**



Scheme 2 *Reagents and conditions*: (a) 1-hexyne, *n*-BuLi, THF, HMPA, –40 °C to 0 °C to –20 °C, 8 h, 84%; (b) KH, 1,3-diaminopropane, r.t., 6 h, 81%.

Next, the synthesis of the chiral C5 hydroxy subunit began from (+)-diethyl tartrate (Scheme 3) which was transformed into alcohol **7** in three steps using a literature procedure.[5] Conversion of alcohol **7** into alkyne **9** took place smoothly via Parikh–Doering oxidation conditions (SO_3·py, DMSO, Et_3N)[6] to aldehyde and subsequent treatment with Ohira–Bestmann reagent **8** under K_2CO_3/MeOH.[7] The terminal alkyne functionality in **9** was then transformed into alkynyl bromide **5** by the reaction with NBS/$AgNO_3$ in acetone.[8]

With the required fragments **4** and **5** in hand, our anticipated plan was to use Cadiot–Chodkiewicz coupling reaction to couple these two units.[9] Thus, the reaction of alkyne **4** with alkynyl bromide **5** in the presence of CuCl (2 mol%), NH_2OH×HCl, 30% *n*-$BuNH_2$ in H_2O provided

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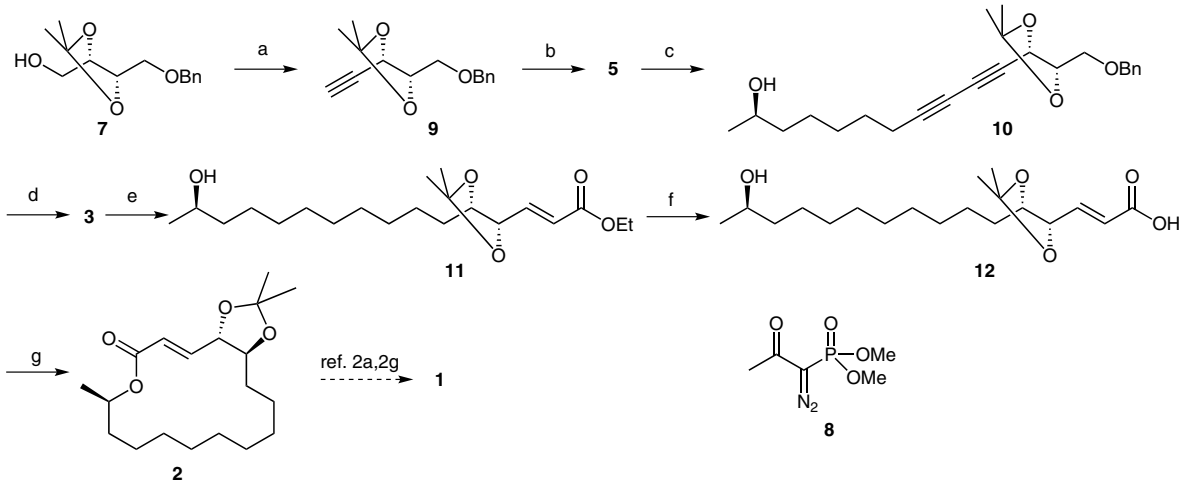

Scheme 3 *Reagents and conditions*: (a) (i) SO_3·py, DMSO, Et_3N, CH_2Cl_2, 0 °C, 1 h; (ii) **8**, K_2CO_3, MeOH, r.t., 12 h, 89%; (b) NBS, $AgNO_3$, acetone, 0 °C to r.t., 30 min, 93%; (c) 4, *n*-$BuNH_2$, NH_2OH·HCl, CuCl, 0 °C to r.t., 1 h, 78%; (d) H_2, 10% Pd/C, EtOH, r.t., 36 h, 84%; (e) TEMPO, BAIB, PPh_3=$CHCO_2Et$, CH_2Cl_2, r.t. to 0 °C to r.t., 3 h, 78%; (f) LiOH, THF–H_2O (1:1), r.t., 12 h, 99%; (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, 0 °C, 2 h, DMAP, toluene, 100 °C, 12 h, 87%.

the coupled product **10** in 78% yield. Diyne **10** underwent clean saturation under standard hydrogenation conditions (H_2, 10% Pd/C in EtOH) to afford diol **3** in 84% yield.

Selective oxidation of primary hydroxyl group of **3** to aldehyde (BAIB/TEMPO) and subsequent one-pot Wittig olefination with a stable two-carbon ylide (Ph_3P=$CHCO_2Et$) provided the α,β-unsaturated ester **11** in 78% yield.[10] The ester was then hydrolyzed under LiOH conditions, and the resulting hydroxy acid **12** was subjected to Yamaguchi macrolactonization[11] to get the desired macrolactone **2** in 87% yield (Scheme 3).[12] This macrolactone has previously been used to accomplish the synthesis of (–)-A26771B.[2a,g]

In conclusion, this convergent formal synthesis of (–)-A26771B is achieved in seven steps in the longest linear sequence from the (*R*)-propylene oxide with 29.9% overall yield. This approach relies on the use of two alkyne fragments, which were easily obtained from (*R*)-propylene oxide and (+)-diethyl tartrate. The present route provides a useful showcase of alkyne-assisted strategy through zipper reaction, Cadiot–Chodkiewicz coupling, and Yamaguchi macrolactonization in the synthesis of macrolides.

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References and Notes

(1) Michel, K. H.; Demoarco, P. V.; Nagarajan, R. *J. Antibiot.* **1977**, *30*, 571.
(2) For enantioselective synthesis, see: (a) Gebauer, J.; Blechert, S. *J. Org. Chem.* **2006**, *71*, 2021. (b) Lee, W.; Shin, H. J.; Chang, S. *Tetrahedron: Asymmetry* **2001**, *12*, 29. (c) Kobayashi, Y.; Okui, H. *J. Org. Chem.* **2000**, *65*, 612. (d) Nagarajan, M. *Tetrahedron Lett.* **1999**, *40*, 1207. (e) Sinha, S. C.; Sinha-Bagchi, A.; Keinan, E. *J. Org. Chem.* **1993**, *58*, 7789. (f) Quinkert, G.; Kueber, F.; Knauf, W.; Wacker, M.; Koch, U.; Becker, H.; Nestler, H. P.; Durner, G.; Zimmermann, G.; Bats, J. W.; Egert, E. *Helv. Chim. Acta* **1991**, *74*, 1853. (g) Tatsuta, K.; Amemiya, Y.; Kanemura, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 3248. For racemic synthesis, see: (h) Trost, B. M.; Brickner, S. J. *J. Am. Chem. Soc.* **1983**, *105*, 568. (i) Fujisawa, T.; Okada, N.; Takeuchi, M.; Sato, T. *Chem. Lett.* **1983**, 1271. (j) Asaoka, M.; Abe, M.; Mukuta, T.; Takei, H. *Chem. Lett.* **1982**, 215. (k) Asaoka, M.; Yanagida, N.; Takei, H. *Tetrahedron Lett.* **1980**, *21*, 4611.
(3) (a) Reddy, Ch. R.; Rao, N. N. *Tetrahedron Lett.* **2009**, *50*, 2478. (b) Reddy, Ch. R.; Srikanth, B. *Synlett* **2010**, 1536.
(4) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Kimmel, T.; Becker, D. *J. Org. Chem.* **1984**, *49*, 2494.
(5) Horvath, A.; Benner, J.; Backvall, J.-E. *Eur. J. Org. Chem.* **2004**, 3240.
(6) Parikh, J. R.; Doering, W. v. E. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(7) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synlett* **1996**, 521. (c) Roth, G. J.; Bernd, L.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59.
(8) Hofmeister, H.; Annen, K.; Laurent, H.; Weichert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.
(9) (a) Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819. (b) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**, 597.
(10) Vatele, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715.
(11) Inanaga, J.; Hirata, K.; Sacki, H.; Hatsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(12) **Spectral Data of Representative New Compounds**
Compound **9**: $[\alpha]_D^{20}$ –24.8 (*c* 1.0, $CHCl_3$). IR (KBr): ν_{max} = 2989, 2933, 2864, 2121, 1726, 1635, 1454, 1376, 1241, 1214, 1086, 852, 740, 398 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.27 (m, 5 H), 4.59 (s, 2 H), 4.49 (dd, *J* = 2.2, 6.8 Hz, 1 H), 4.25–4.18 (m, 1 H), 3.60 (d, *J* = 4.5 Hz, 2 H), 2.44 (d, *J* = 2.2 Hz, 1 H), 1.48 (s, 3 H), 1.41 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.5, 128.3, 127.7, 127.6, 110.8, 80.8, 80.6, 74.6, 73.5, 68.9, 67.1, 26.8, 26.0. ESI-

HRMS: *m/z* calcd for $C_{15}H_{18}O_3Na$ $[M + Na]^+$: 269.1153; found: 269.1146.

Compound **5**: $[\alpha]_D^{20}$ –43.0 (*c* 1.0, $CHCl_3$). IR (KBr): ν_{max} = 2988, 2926, 2214, 1722, 1626, 1376, 1217, 1081, 1022, 851, 742, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.27 (m, 5 H), 4.59 (s, 2 H), 4.53 (d, *J* = 7.5 Hz, 1 H), 4.35–4.18 (m, 1 H), 3.59 (d, *J* = 4.5 Hz, 2 H), 1.48 (s, 3 H), 1.41 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 128.3, 127.6, 127.5, 110.8, 80.4, 76.9, 73.4, 68.9, 68.0, 47.1, 26.8, 26.0. ESI-MS: *m/z* = 347 $[M + Na]^+$.

Compound **10**: $[\alpha]_D^{20}$ –59.9 (*c* 1.0, $CHCl_3$). IR (KBr): ν_{max} = 3426, 2932, 2861, 2254, 1718, 1633, 1454, 1375, 1219, 1087, 1035, 851, 741, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 4.57 (s, 2 H), 4.55 (d, *J* = 6.8 Hz, 1 H), 4.25–4.18 (m, 1 H), 3.80–3.71 (m, 1 H), 3.58 (d, *J* = 4.5 Hz, 2 H), 2.29 (t, *J* = 6.8 Hz, 2 H), 1.60–1.36 (m, 8 H), 1.47 (s, 3 H), 1.40 (s, 3 H), 1.17 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 128.2, 127.5, 127.4, 110.7, 81.9, 80.5, 73.3, 72.0, 71.3, 68.9, 67.6, 67.6, 64.3, 38.8, 28.5, 27.8, 26.7, 25.9, 24.9, 23.2, 18.9. ESI-MS: *m/z* = 407 $[M + Na]^+$.

Compound **3**: $[\alpha]_D^{20}$ –20.7 (*c* 1.0, $CHCl_3$). IR (KBr): ν_{max} = 3413, 2926, 2856, 1631, 1455, 1374, 1220, 1049, 851, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.85–3.80 (m, 1 H), 3.74 (dd, *J* = 3.0, 12.0 Hz, 2 H), 3.68–3.63 (m, 1 H), 3.54 (dd, *J* = 4.0, 12.0 Hz, 1 H),1.56–1.25 (m, 18 H), 1.38 (s, 3 H), 1.37 (s, 3 H), 1.17 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 108.4, 81.5, 76.9, 68.0, 62.0, 39.2, 33.0, 29.55, 29.51, 29.4, 29.3, 27.2, 26.9, 25.8, 25.6, 23.3. ESI-HRMS: *m/z* calcd for $C_{17}H_{34}O_4Na$ $[M + Na]^+$: 325.2354; found: 325.2363.

Compound **11**: $[\alpha]_D^{20}$ –10.3 (*c* 1.6, $CHCl_3$). IR (KBr): ν_{max} = 3452, 2938, 2855, 1722, 1655, 1373, 1300, 1260, 1169, 1042, 771, 555 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.83 (dd, *J* = 5.0, 15.0 Hz, 1 H), 6.08 (d, *J* = 15.0 Hz, 1 H), 4.21 (q, *J* = 7.0 Hz, 2 H), 4.11 (t, *J* = 7.0 Hz, 1 H), 3.80–3.73 (m, 1 H), 3.69 (q, *J* = 7.0 Hz, 1 H), 1.61–1.54 (m, 2 H), 1.51–1.22 (m, 16 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.31 (t, *J* = 7.0 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.0, 144.1, 122.5, 109.2, 80.5, 80.1, 68.0, 60.5, 39.2, 32.0, 29.5, 29.4, 29.3, 27.2, 26.5, 25.8, 25.6, 23.4, 14.1. ESI-HRMS: *m/z* calcd for $C_{21}H_{38}O_5Na$ $[M + Na]^+$: 393.2616; found: 393.2627.

Compound **2**: $[\alpha]_D^{20}$ +5.6 (*c* 0.78, $CHCl_3$). IR (KBr): ν_{max} = 2928, 2856, 1715, 1458, 1374, 1257, 1177, 1055, 987, 862 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.88 (dd, *J* = 7.0, 16.0 Hz, 1 H), 6.12 (d, *J* = 16.0 Hz, 1 H), 5.07–4.99 (m, 1 H), 4.13 (t, *J* = 7.0 Hz, 1 H), 3.78–3.72 (m, 1 H), 1.86–1.77 (m, 1 H), 1.69–1.58 (m, 2 H), 1.53–1.41 (m, 2 H), 1.43 (s, 3 H), 1.42 (s, 3 H), 1.35–1.18 (m, 13 H), 1.26 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 144.3, 123.6, 109.2, 80.7, 80.0, 71.1, 35.2, 31.0, 27.8, 27.2, 27.1, 26.9, 26.5, 26.4, 24.7, 23.3, 20.5. ESI-HRMS: *m/z* calcd for $C_{19}H_{32}O_4Na$ $[M + Na]^+$: 347.2198; found: 347.2206.

