A Diastereoselective Synthetic Approach towards the Synthesis of Berkeleylactone F and Its 4-epi-Derivative

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OMOM
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OTBDMS
8 steps
synthetic intermediate
stereospecific
directional
C-alkylation
of heptadiyne
stereoselective
directional
C-alkylation
of heptadiyne
(1,6-heptadiyne)

Abstract A diastereoselective approach to the synthesis of berkeleylactone F is presented. The synthetic strategy is initiated with commercially available (R)-glycidol, 1,6-heptadiyne, and (R)-methyl lactate. The key feature of the approach is directional functionalization at both terminals of 1,6-heptadiyne.

Key words macrolide, epoxide, ring opening, heptadiyne

Macrolides constitute a class of differently functionalized organic molecules with a minimum ten-membered lactone ring. Such compounds are among the most clinically effective antibiotics, interfering with bacterial protein synthesis, and inhibiting cell growth. However, pathogens have developed resistance against certain antibiotic macrolides due to their extensive use. Thus, structural modification of the existing macrolides and the search for novel macrolides from natural resources may help to continue the fight against infectious diseases. Macrolides have drawn attention of biologists, medicinal chemists and synthetic organic chemists due to their wide scope of applications.1

There are several 16-membered macrolactones with promising biological activities.2 However, the well-known macrolide A26771B3 and recently explored aspergillide D4 and berkeleylactone A–H5 are some of the simple 16-membered macrolides that also exhibit impressive antibacterial activity. Aspergillide D and berkeleylactones A–H were isolated from the culture broth of a marine-derived fungus Aspergillus sp. SCGAF 00764a and from the co-culture fermentation of two fungal species Penicillium fuscum and Penicillium camembertii/clavigerum,5a respectively. Berkeleylactone F showed moderate inhibitory activity against CCRF-CEM leukemia cells. Several efforts by synthetic organic chemists for the synthesis of A26771B3b–e and aspergillide D3b–d have been reported. However, there have been fewer attempts towards the synthesis of the recently disclosed berkeleylactone derivatives, even though they possess promising antimicrobial activities with attractive stereochemical and functional diversity. Syntheses of berkeleylactone A and berkeleylactone F have been reported recently.3b,c Berkeleylactone C, E, and H also show impressive biological activity (Figure 1).5a

Figure 1 Macrolactones with promising biological activities
We selected Berkeleylactone F as the target molecule to explore ways to improve the methodology in our initiative for the general synthesis of 16-membered macroolides. Our main focus was to develop a generalized synthetic strategy for the synthesis of macroolides, involving fewer synthetic steps starting from commercially available materials.

The retrosynthetic strategy for Berkeleylactone F is shown in Scheme 1. Cyclization leading to compound 1d can be achieved by ring-closing metathesis (RCM) of compound 2.

The precursor, compound 2 for RCM can be obtained by the oxidation of alcohol 8, followed by vinylation and chloromethyl methyl etherification (MOM). Silyl group deprotection followed by acrylation of the secondary hydroxyl group are necessary to reach compound 2 starting from compound 8. Removal of the benzyl group and reduction of the alkenes of compound 7 in the same step will lead to compound 8. Further disconnections lead to the starting materials, protected (R)-glycidol 3, protected (R)-methyl lactate (II) and 1,6-heptadiyne (Scheme 1).

A long aliphatic chain together with a hydroxyl functionality are major parts of any macroalactone ring. The use of long-chain terminal diols or terminal alkynes followed by a zipper reaction are the most commonly used strategies to generate the macroalactone. However, these strategies can be quite lengthy. Herein, we report the use of 1,6-heptadiyne to construct the aliphatic chain of the macroalactone. Two-directional C-alkylation of 1,6-heptadiyne with an epoxide and aldehyde, respectively, will introduce the hydroxyl functionalities to the macroalactone ring. There are reports of such applications of diynes in the total synthesis of natural products but they have not previously been applied in the synthesis of macroalactones.

We initiated our synthesis with commercially available 1,6-heptadiyne and (R)-glycidol. The free hydroxyl group of (R)-glycidol was benzylated using benzyl bromide in the presence of sodium hydride in N,N-dimethylformamide as solvent to produce benzylated (R)-glycidol 3. 1,6-Heptadiyne was treated with n-Buli followed by BF₃·OEt2 and subsequently reacted with benzylated glycidol 3 at –78 °C to furnish compound 4. It was interesting to observe that epoxide ring opening of 3 takes place regioselectively to afford desired compound 4 in good yield after two hours. However, the disubstituted by-product was also generated in small amounts after running the reaction for extended periods. This minor by-product could be readily separated by column chromatography from the desired product 4.

Compound 4 was converted into MOM ether 5 using chloromethyl methyl ether in the presence of N,N-diisopropylmethylethylamine in CH₂Cl₂. Compound 5 was treated with n-Buli at –78 °C to generate the corresponding alkynyl lithium derivative, which was allowed to react in situ with (R)-2-(tert-butyldimethylsilyloxy)propanal (I) derived from commercially available (R)-(−)-methyl lactate using DIBAL-H in anhydrous hexane at –78 °C at the same temperature to produce the Felkin model controlled product in 80% yield, producing the anti-isomer 6 exclusively. The observed high diastereoselectivity is in complete agreement with the report of Léséleuc et al.

Other reports for the nucleophilic addition of alkynyl lithium to optically active aldehydes derived from lactate also strongly support the proposed outcome (Scheme 2).

The highly diastereoselective preference for the anti-product may be explained by the non-chelating Felkin–Anh model, as shown in Figure 2. In accordance with the model, the electron-withdrawing group as well as the sterically hindered bulky OTBS group are preferentially placed anti to the carbonyl group in the presence of non-chelating cations such as Li⁺. The oxygen atom of the OTBS group at the α-position of the aldehyde is unable to chelate with the carbonyl oxygen in the presence of the poor chelating cation Li⁺. Nucleophilic attack takes place from the side of smallest group (H). As a result, the OTBS group at the α-position to the aldehyde induces the anti stereochemistry (Figure 2).
The free hydroxyl group of compound 6 was transformed into the corresponding MOM ether using chloromethyl methyl ether in the presence of N,N-diisopropylethylamine to produce compound 7 (Scheme 2).

One-pot reduction of the C–C triple bonds and deprotection of the benzyl group of 7 was achieved by hydrogenation over Pd/C in methanol,11 which afforded 8 in good yield. The primary hydroxyl group of the latter was oxidized using pyridinium chlorochromate in the presence of 4 Å molecular sieves at room temperature. The crude aldehyde obtained after work up was directly subjected to chelation-controlled vinylolation using vinyl magnesium bromide obtained after work up was directly subjected to chelation-controlled vinylolation using vinyl magnesium bromide in THF at −78 °C to produce an inseparable mixture of 9 (syn:anti = 5:1, determined by 1H NMR analysis; Scheme 3). The diastereoselectivity of the syn-isomer over the anti-isomer is in good agreement with literature precedent.12 The syn-selectivity may be explained by considering Cram’s chelate model as shown in Figure 3.

In accordance with the Cram chelate model, the MOM group is placed syn- to carbonyl group in the presence of the chelating Mg2+. Nucleophilic attack at the carbonyl group in the chelated substrate takes place from the side of the smallest group (Figure 3). The syn-selectivity is consistent with previous reports for vinylolation of aldehydes with an α-MOM group.10,12c,d,h

Compound 9 was treated with methoxymethyl chloride in the presence of N,N-diisopropylethylamine to produce compound 10 in a 5:1 syn/anti ratio (Scheme 3). We were unable to separate this diastereomeric mixture at this stage. Recently Reddy et al. completed the total synthesis of berkeleylactone F 1d via the minor isomer 10b obtained in our strategy (Scheme 4).5c Reddy et al. used asymmetric epoxidation as a key step to introduce the asymmetric centre.

Thus, the present synthesis of compounds 10a and 10b, which was achieved in eight steps in 12% yield, leads to the formal synthesis of 4-epi-berkeleylactone F and berkeleylactone F, respectively (Scheme 5).

In summary, we present a synthesis of berkeleylactone F and its C-4 epi-isomer starting from commercially available 1,6-heptadiyne and optically active (R)-glycidol.13,14 The important feature of the synthesis is the application of 1,6-heptadiyne in directed C-alkylation functionalization at both ends of the diyne; which is the first time such an approach has been used in 16-membered macrolactone syn-
thesis. In addition, our strategy involves fewer steps toward the synthesis of berkeleylactone F and its 4-epi-derivative than previous approaches.

Funding Information
The Department of Science and Technology, Ministry of Science and Technology, India (INSPIRE Faculty Award- IFA 12-CH 45) is gratefully acknowledged for financial support.

Acknowledgment
The authors acknowledge NIT Sikkim & TEQIP III for infrastructure support and Dr. Sajal Das, NBU and Tapan Kumar Kuiyia, Sandip Guchhait, Joyanta Mondal, Sousik Bardhan, Susanta Mandal for constant support.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707305.

References and Notes

Supported by the INSPIRE Faculty Award-IFA 12-CH 45. Funding Information
The authors acknowledge NIT Sikkim & TEQIP III for infrastructure support and Dr. Sajal Das, NBU and Tapan Kumar Kuiyia, Sandip Guchhait, Joyanta Mondal, Sounik Bardhan, Susanta Mandal for constant support.

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(4.6 mL, 4.6 mmol, 1.0 M in hexane 1 equiv). The resulting mixture was stirred for 30 min at this temperature and a solution of epoxide 3 (250 mg, 1.52 mmol, 0.33 equiv, dissolved in anhydrous THF, 5 mL) was added dropwise, followed by rapid addition of BF$_3$·Et$_2$O (freshly distilled, 0.6 mL, 6.66 mmol, 1.45 equiv). The reaction mixture was stirred for 1.5 h and then quenched with saturated aqueous NH$_4$Cl solution and extracted with Et$_2$O (3 × 20 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under vacuum. The crude material was purified by column chromatography on silica gel (10% EtOAc in pet ether (PE)) to give pure alcohol 4 (0.88 g, 3.43 mmol 75%) as a yellow oily liquid. TLC: $R_f$ 0.76 (10% EtOAc in PE). IR: 1096, 1428, 1633, 2115, 2946, 3453 cm$^{-1}$. 1H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.71 (p, $J$ = 7.0 Hz, 2 H), 1.99 (t, $J$ = 2.6 Hz, 1 H), 2.28–2.33 (m, 4 H), 2.42–2.46 (m, 2 H), 3.52 (dd, $J_{1,2}$ = 3.92 Hz, $J_{1,3}$ = 9.52 Hz, 1 H), 3.61 (dd, $J_{1,2}$ = 6.68 Hz, $J_{1,3}$ = 9.52 Hz, 1 H), 4.59 (s, 2 H), 7.30–7.40 (m, 5 H). 13C NMR (100 MHz, CDCl$_3$): $\delta$ = 17.5, 17.8, 23.9, 27.7, 68.8, 69.2, 72.9, 73.4, 76.4, 81.4, 83.5, 128.3, 137.9. HRMS: $m/z$ [M + Na]$^+$ calcd for C$_{17}$H$_{20}$O$_2$Na: 279.1361; found: 279.1361.

(14) Synthesis of (5S,14S,15R)-5-((Benzyloxy)methyl)-15,17,18,18-pentamethyl-2,4,16-trioxa-17-silanonadeca-7,12-diyn-14-ol (6): (R)-(+)-Methyl lactate (1.0 g, 9.60 mmol, 1 equiv), was dissolved in anhydrous DMF (5 mL), and imidazole (1.06 g, 15.57 mmol, 1.6 equiv) was added. The solution was cooled in an ice bath and TBSCl (1.45 g, 9.60 mmol, 1 equiv) was added slowly in portions. After the completion of addition, the ice bath was allowed to melt gradually overnight. After 18 h, the reaction mixture was diluted with water (3 mL) and hexanes (10 mL). The aqueous phase was separated and extracted with hexanes (60 mL), and the combined organic extract was washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated by rotary evaporation to afford the TBS ether (1.6 g, 7.33 mmol, 76%) as a colorless liquid, which was used without purification. The above prepared TBS protected (R)-(+)-methyl lactate (1.00 g, 4.58 mmol, 1 equiv), in hexanes (20 mL), was cooled to –78 °C, DIBAL-H (4.7 mL, 1.0 M in hexanes, 4.7 mmol, 1.0 equiv) was added dropwise and the mixture was stirred for 45 minutes at –78 °C. The reaction mixture was then quenched by addition of MeOH (1.0 mL) and stirred for 15 min at –78 °C. The cold solution was transferred to a round-bottom flask containing saturated aqueous Rochelle salt (10 mL) and the resulting mixture was vigorously stirred for 30 min. The aqueous phase was separated and extracted with hexanes, and the combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated to afford the aldehyde (0.70 g, 3.66 mmol, 80%) as a colorless liquid.

To a solution of compound 5 (0.90 g, 3.0 mmol, 1 equiv) in anhydrous THF (15 mL), n-BuLi (.3.0 mL, 3.0 mmol, 1 M in THF, 1 equiv) was added dropwise at –78 °C. The solution was stirred for 30 min at the same temperature and then freshly prepared aldehyde was added to the reaction mixture dropwise (0.70 g, 3.66 mmol, 1.2 equiv over 30 mins) and the mixture was stirred for 2.5 h. The reaction mixture was quenched with saturated aqueous NH$_4$Cl and the organic phase was separated and evaporated under reduced pressure. The aqueous layer was extracted with EtOAc and the organic extract was washed with brine, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated by rotary evaporation. Column chromatographic purification (10% EtOAc in PE) of the resultant crude residue provided pure alcohol 6 (1.20 g, 2.45 mmol, 80%) as a pale-yellow liquid. TLC: R$_f$ 0.67 (% EtOAc in PE), IR: 1252, 1494, 1628, 2245, 2985, 3470 cm$^{-1}$. 1H NMR (400 MHz, CDCl$_3$): $\delta$ = 0.11 (s, 3 H), 0.12 (s, 3 H), 0.92 (s, 9 H), 1.24 (d, $J$ = 6.24 Hz, 3 H), 1.59 (brs, 1 H), 1.68 (p, $J$ = 6.43 Hz, 2 H), 2.24–2.37 (m, 4 H), 2.48–2.53 (m, 2 H), 3.41 (s, 3 H), 3.62–3.64 (m, 2 H), 3.86–3.94 (m, 2 H), 4.28 (m, 1 H), 4.59 (s, 2 H), 4.77 (s, 2 H), 7.30–7.37 (m, 5 H). 13C NMR (100 MHz, CDCl$_3$): $\delta$ = –4.7, –4.4, 17.9, 22.2, 25.8, 27.9, 55.5, 67.1, 71.2, 71.6, 73.4, 74.8, 78.6, 80.9, 85.8, 95.9, 127.6, 127.6, 128.4, 138.2. HRMS: $m/z$ [M + Na]$^+$ calcd for C$_{28}$H$_{44}$O$_5$SiNa: 511.7212; found: 511.7211.