Enantioselective total synthesis of a novel polyketide natural product (+)-integrasone, an HIV-1 integrase inhibitor†

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Enantioselective total synthesis of the recently isolated, novel polyketide natural product (+)-integrasone has been accomplished from the readily available Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone. An enzymatically desymmetrized epoxyquinone building block has been elaborated through a series of regio- , chemo- and stereocontrolled steps to the final bicyclic framework of the natural product.

HIV-1 protease, reverse transcriptase and integrase are the three critical enzymes implicated in viral replication and their inhibition is the key to various AIDS therapies.[1] Early AIDS therapies have targeted protease and reverse transcriptase viral proteins and clinical agents based on their inhibition have made a great impact on both viral spread and the life expectancy of AIDS patients.[2] However, the problem of toxicity of these anti-retroviral agents and emergence of drug resistance necessitates a continued search for new targets.[3] This quest has led to renewed interest in the retroviral encoded protein integrase, which is required for the insertion of HIV-1 proviral DNA into the host genome.[4] This process is mediated by integrase in three steps involving assembly, endonucleolytic processing of the viral DNA ends and strand transfer or joining of the viral and cellular DNAs. Since HIV-1 integrase is not present in the host cell but is essential for replication, its inhibition constitutes a promising lead strategy for developing new anti-retroviral agents for therapeutics.[5,6] In view of this potential, natural products and synthetic compounds are being extensively searched and screened for this purpose. Typical examples of such integrase inhibitors are the natural sesquiterpenoid integric acid **1**[7] and the Merck compound L-870,812 **2**.[5,6]

Early in 2004, scientists at Merck reported[8] the isolation and absolute structure determination of a polyketide derived and epoxyquinone based natural product integrasone **3** from an unidentified sterile mycelium. **3** has been shown to inhibit the strand transfer reaction of HIV-1 integrase with an IC_{50} of 41 μM.[8] The attributes of structural novelty with stereochemical nuances, coupled with promising integrase inhibitory profile, makes integrasone **3** an attractive synthetic target. Our interest in the synthesis of **3** was spontaneous on account of an ongoing research program in the group on the synthesis of biologically active epoxyquinone natural products.[9,10] Herein, we report the first total synthesis of the natural integrasone (+)-**3**, following a short, simple approach, which is also diversity oriented.

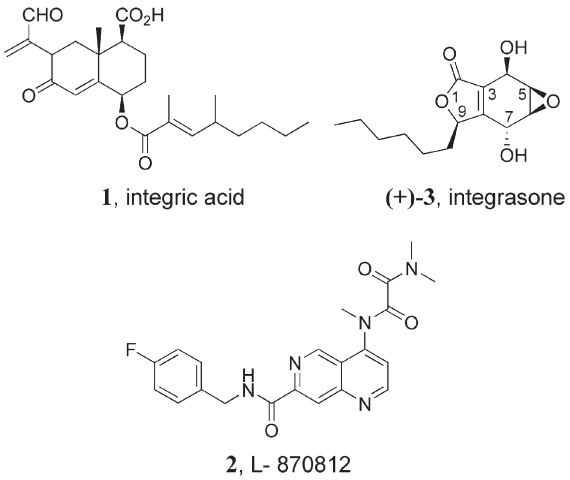
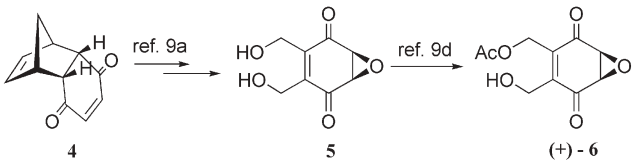
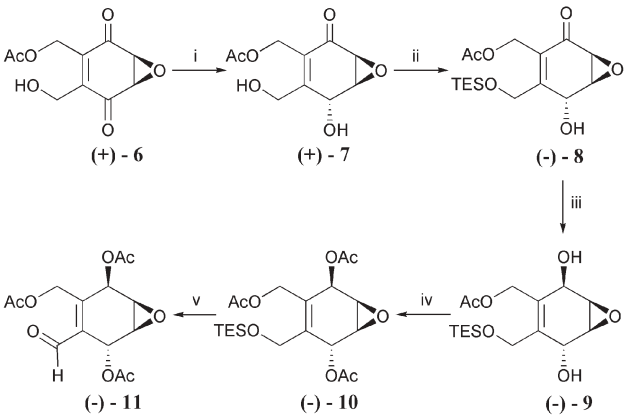


Fig. 1



Scheme 1



Scheme 2 *Reagents and conditions:* i, DIBAL-H, THF, −78 °C, 30 min, 78%; ii, TESCl, py, −15 °C, 25 min, 70%; iii, $NaBH_4$, MeOH, −55 °C, 20 min, 85%; iv, Ac_2O, py, DMAP, rt, 97%; v, PCC-silica gel, rt, 80%.

† Electronic supplementary information (ESI) available: spectral data and copies of the ^1H and ^{13}C spectra (17 pages) of selected intermediates. See http://www.rsc.org/suppdata/cc/b5/b502024g/

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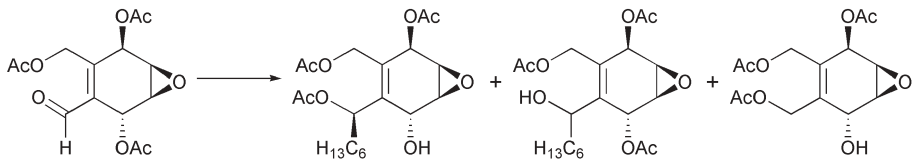
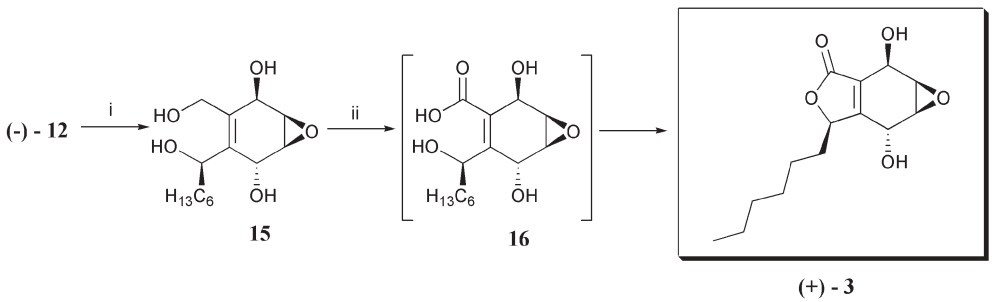


Scheme 3 *Reagents and conditions:* $C_6H_{13}MgBr$, THF, −10 °C, 30 min.



Scheme 4 *Reagents and conditions:* i, K_2CO_3, MeOH, 0 °C, 85%; ii, TEMPO, NaOCl, $NaClO_2$, NaH_2PO_4, 4 h, 50%.

Our synthetic pursuit of integrasone (+)-**3** emanated from the readily available Diels–Alder adduct **4** of cyclopentadiene and *p*-benzoquinone, which can be conveniently elaborated to *meso*-**5** in two steps involving epoxidation of the 1,4-enedione moiety followed by two carbon–carbon bond connectivities through double hydroxymethylation.[9a] Further, we have recently demonstrated an efficient protocol for the desymmetrization of **5** through enzymatic transesterification to furnish enantiomerically pure (+)-**6** (>99% ee)[9d] and this monoacetate served as the key building block for the synthesis of integrasone **3** (Scheme 1).

The first task *en route* to **3** was to effect stereoselective carbonyl group reductions in (+)-**6** to generate the requisite hydroxyl stereochemistry at C4 and C7 present in the natural product. DIBAL-H reduction of **6** was regio- and stereoselective at C7, directed by the free primary hydroxyl group and the epoxide oxygen, to furnish (+)-**7** as a single product.[9e,11] The primary hydroxyl group in **7** was selectively TES-protected to give **8** and further stereoselective sodium borohydride reduction of the C4 carbonyl group from the face opposite to the epoxide ring furnished the diol **9**,[11] (Scheme 2). The two hydroxyl groups at C4 and C7 in **9** were readily protected as the diacetate **10**[11] and direct PCC oxidation[12] led to aldehyde **11**[11] through TES deprotection and oxidation of the primary hydroxyl group.

At this stage the cyclohexyl side arm present in the natural product needed to be installed at C9 with concomitant placement of the key hydroxyl group required for the γ-lactone ring formation.

Consequently aldehyde **11** was treated with hexylmagnesium bromide and the reaction to our delight was highly stereoselective to furnish **12**[11] and **13** (10:1), although in a modest ~40% overall yield. In addition, the triacetate **14** (42%) was also obtained through the reduction of aldehyde **11** and acetate migration, (Scheme 3).[13] The stereoselectivity leading to the preferred formation of the triacetate **12** during the Grignard addition could be a consequence of the directing influence of the C7 acetate group, which subsequently migrates to C9 position.

The stage was now set for the end game to deliver the natural product. Careful base hydrolysis in **12** delivered the highly polar tetrol **15**[11] which was subjected to selective oxidation of the primary hydroxyl functionality with sodium chlorite catalyzed by TEMPO and bleach.[14] Quite remarkably, this reaction directly furnished integrasone (+)-**3** in 50% isolated yield through the concomitant cyclization of the proposed carboxylic acid intermediate[15] **16**, (Scheme 4). The identity of our synthetic material was fully established through the comparison of the ^1H and ^{13}C NMR spectra[11] and specific rotation, $[\alpha]_D$ +16.6 (*c* 0.36, MeOH) with that of the natural product, *lit.*[8] $[\alpha]_D$ +16.7 (*c* 1.5, MeOH).

In summary, we have accomplished a short, simple enantioselective total synthesis of the recently reported integrase inhibitor integrasone (+)-**3** from readily available building blocks. Besides confirming the absolute configuration of the natural product, the synthesis is intrinsically diversity oriented and should pave the way for accessing analogues.

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