Pergamon

Tetrahedron Letters 42 (2001) 7867–7871

TETRAHEDRON LETTERS

An enantio- and stereocontrolled route to epopromycin B via *cinchona* alkaloid-catalyzed Baylis–Hillman reaction

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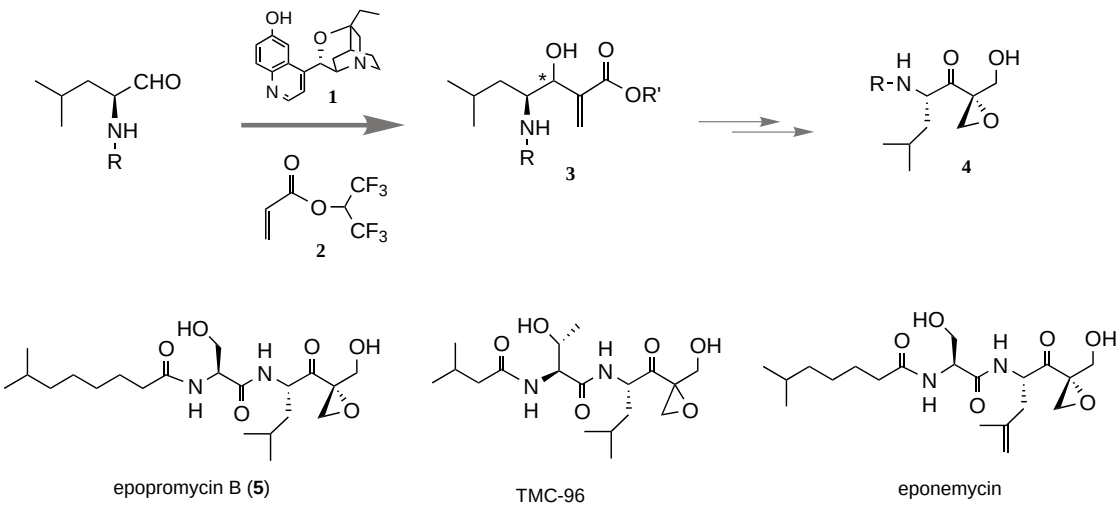
Received 24 August 2001; revised 6 September 2001; accepted 7 September 2001

Abstract—An enantio- and stereocontrolled route to epopromycin B having the epoxy-β-aminoketone pharmacophore is developed based on the *cinchona* alkaloid-catalyzed Baylis–Hillman reaction of *N*-Fmoc-leucinal.

Recently, we have developed a highly enantioselective asymmetric Baylis–Hillman reaction using a chiral amine catalyst **1** derived from quinidine and highly reactive 1,1,1,3,3,3-hexafluoroisopropyl acrylate (**2**).[1] To explore the synthetic utility of our methodology, we envisaged its application towards the synthesis of the epoxy-β-aminoketone moiety **4** of epopromycin B (**5**),[2,3] a novel plant cell wall synthesis inhibitor isolated from the culture broth of *Streptomyces* sp. NK0400. This densely functionalized structural motif is also found in the proteasome inhibitors TMC-86 and TMC-96[4] as well as angiostatic natural product eponemycin,[5] and thus has attracted considerable attention as a promising pharmacophore.[6,7] We describe herein the successful utilization of the *cinchona* alkaloid-catalyzed Baylis–Hillman reaction for the stereoselective construction of the α-methylene–statine framework **3**, and its straightforward transformation to epopromycin B (**5**) (Scheme 1).



Scheme 1.

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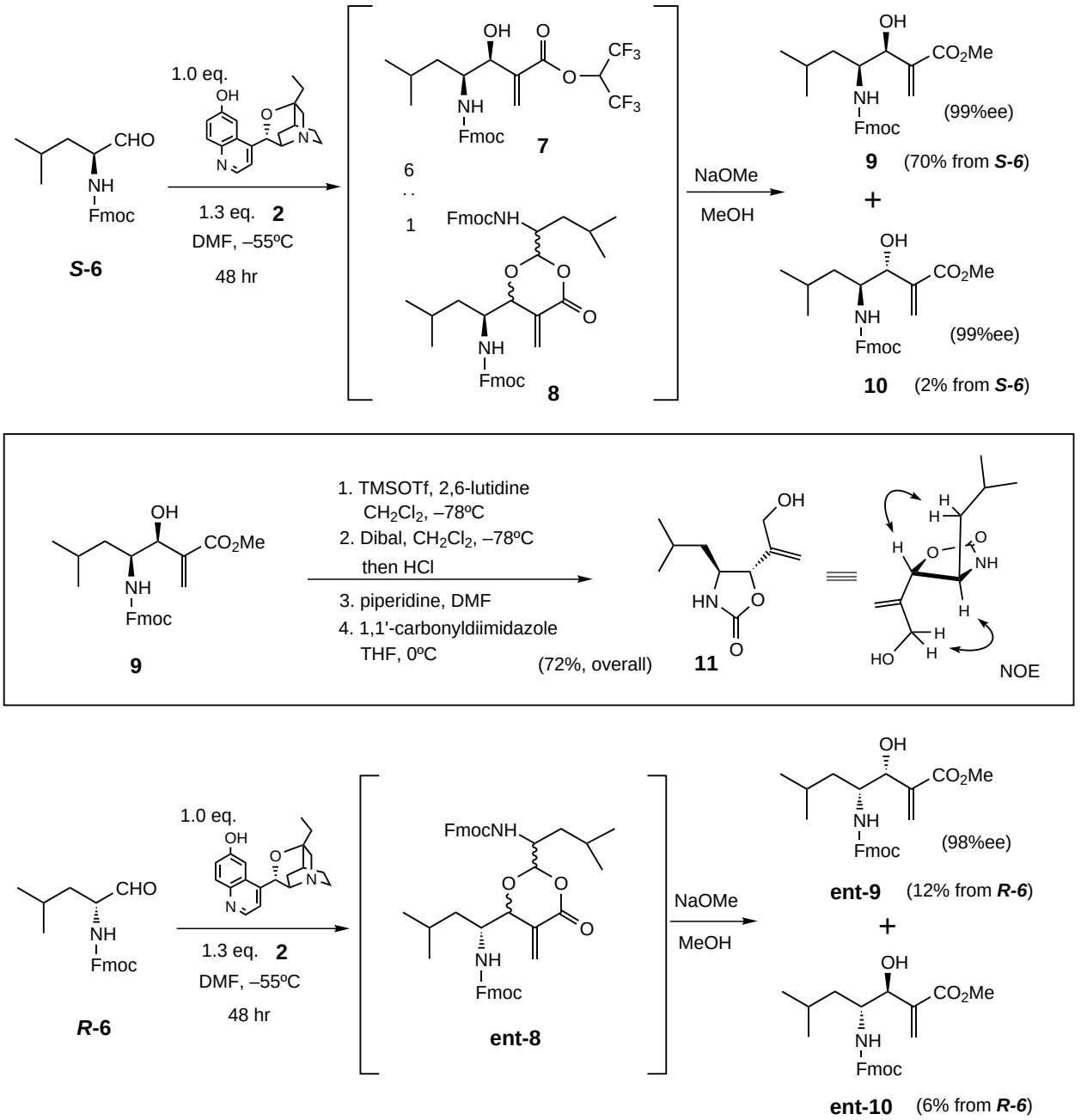
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01676-8

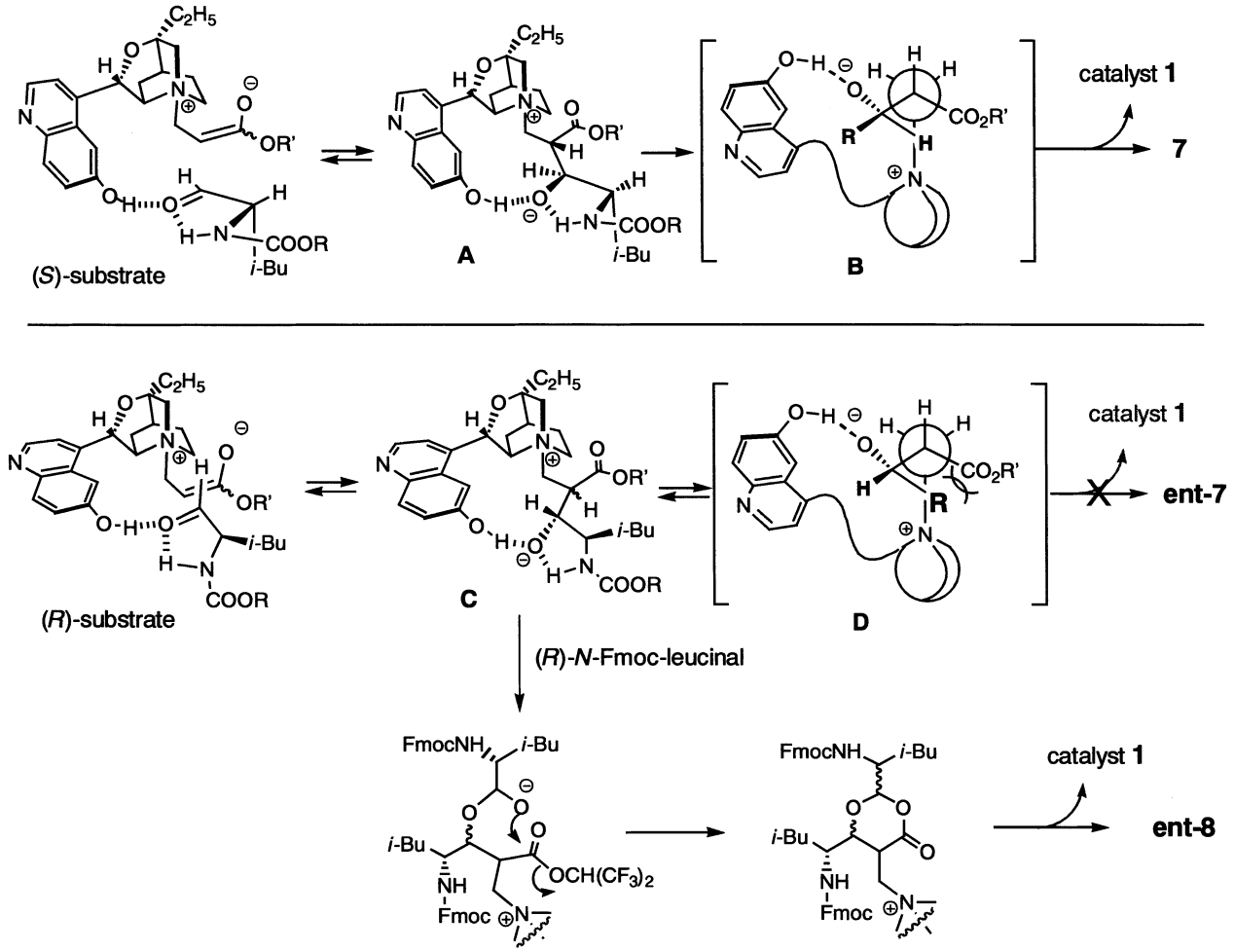
Reaction of (*S*)-*N*-Fmoc-leucinal (***S*-6**)[8] with 1,1,1,3,3,3-hexafluoroisopropyl acrylate (**2**) proceeded smoothly in the presence of a stoichiometric amount of the chiral amine catalyst **1** even at −55°C in DMF to give a 6:1 mixture of the ester **7** and the dioxanone **8**.[1,9] Without separation, this mixture was subjected to methanolysis to give two diastereomeric esters **9**, $[\alpha]_D^{21}$ −7.0° (*c* 1.0, $CHCl_3$), and **10** in 70 and 2% yields, respectively. The *syn*-stereochemistry of the major product **9** was confirmed by NOESY experiment of the cyclic carbamate **11** derived from **9**. HPLC analysis using a chiral column revealed both products were almost enantiomerically pure. It is interesting to note that the enantio-preference (*R*-selectivity)[1] of the chiral amine catalyst **1** matches well with *S*-configuration of the substrate to lead the high *syn*-selectivity.[10]

On the other hand, reaction of (*R*)-*N*-Fmoc-leucinal (***R*-6**) under the same conditions turned out to occur very sluggishly and only a diastereomeric mixture of the dioxanones was obtained in low yield. Methanolysis of the mixture gave *ent*-**9**, $[\alpha]_D^{23}$ +7.2° (*c* 1.1, $CHCl_3$), and *ent*-**10** in 12% and 6% yields in two steps, respectively (Scheme 2).

The following mechanistic consideration would rationalize the observed stereo- and enantioselectivity. (*S*)-*N*-Fmoc-leucinal (***S*-6**) undergoes aldol reaction with the initially formed enolate in accordance with its inherent diastereofacial preference[11] (*si*-face selectivity) to produce betaine intermediate **A** stabilized by an intramolecular hydrogen-bonding network.[12] Since the conformation of **A** is nearly ideal for the subsequent E2



Scheme 2.



Scheme 3.

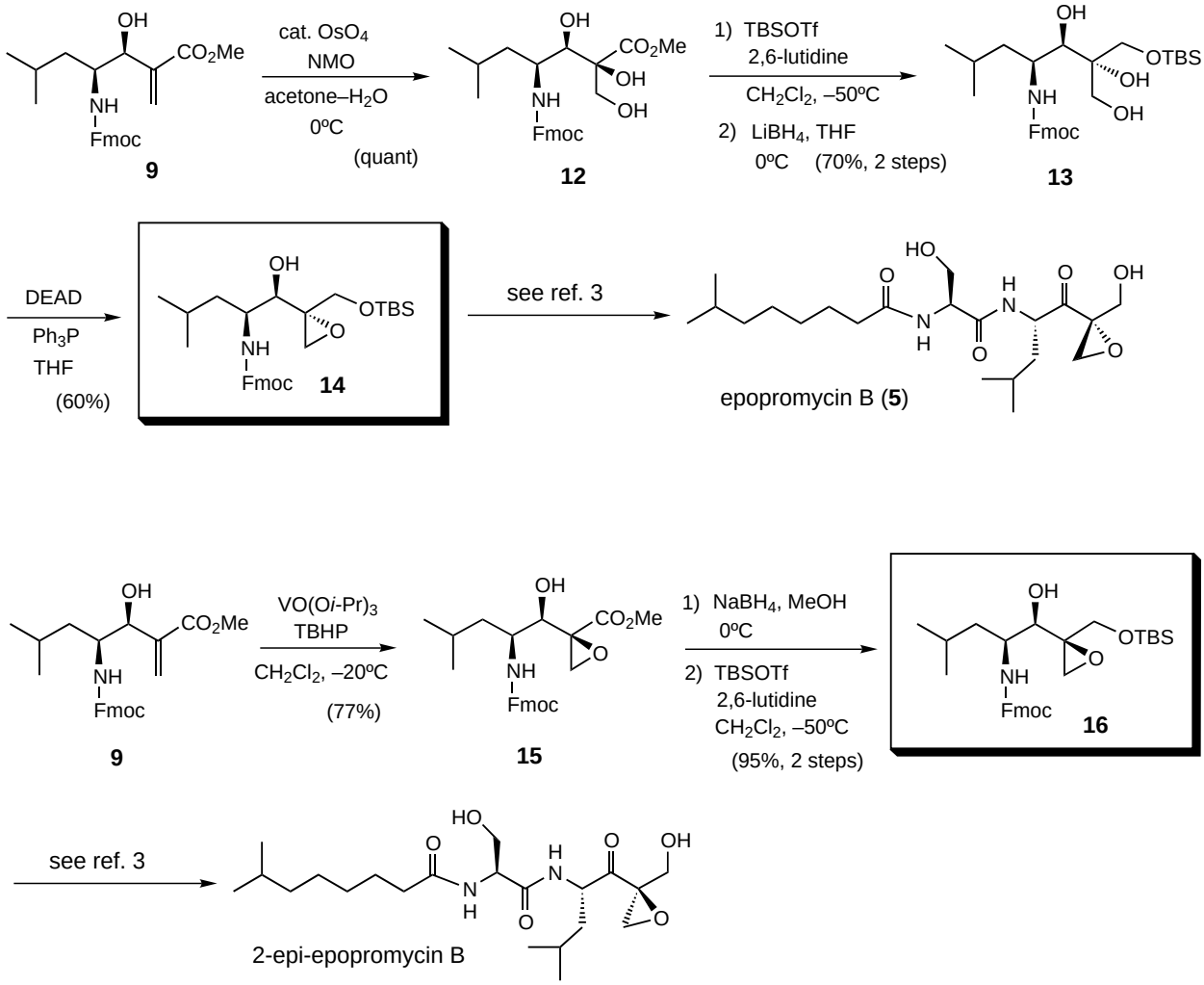
or E1cb reaction for stereoelectronic reasons[13] as depicted in Newman projection **B**, facile elimination giving the *syn*-ester **7**, in turn, takes place. In the case of (*R*)-*N*-Fmoc-leucinal (***R*-6**), this aldehyde allows approach of the enolate from its *re*-face to produce betaine **C**, where the elimination reaction is retarded by the steric interaction as depicted in **D**. Thus, **C** reacts with a second (*R*)-*N*-Fmoc-leucinal (***R*-6**) to form dioxanone *ent*-**8** with releasing a 1,1,1,3,3,3-hexafluoroisopropanol and **1** (Scheme 3).

With the Baylis–Hillman product **9** in hand in almost enantiomerically pure form, we then investigated its stereoselective transformation to the key precursor of epopromycin B. Dihydroxylation of **9** using a catalytic amount of OsO_4 in the presence of NMO[14] proceeded smoothly with complete diastereoselectivity to afford the all-*syn* triol **12** as colorless crystals, mp 179–181°C, $[\alpha]_D^{25}$ −19.3° (*c* 0.21, MeOH), in quantitative yield.[15] Selective protection of the primary hydroxy group of **12** as its TBDMS ether, and reduction of the ester with $LiBH_4$ gave the triol **13**, $[\alpha]_D^{21}$ +9.7° (*c* 0.95, MeOH), in 70% yield. Finally, treatment of the diol **13** with diethyl azodicarboxylate in the presence of triphenylphosphine in THF[16] at 60°C furnished the epoxide **14**, $[\alpha]_D^{26}$ −8.4° (*c* 1.0, $CHCl_3$), the Dobler's key precursor of epopromycin B,[3] in 60% yield. Furthermore, the Baylis–Hillman product **9** was also converted stereoselectively to **16**, $[\alpha]_D^{18}$ −28.8° (*c* 1.6, $CHCl_3$), in 73% in three steps, a key precursor of *epi*-epopromycin B which is known to exhibit other intriguing biological activities[3] (Scheme 4).

In conclusion, we have developed an enantio- and stereocontrolled route to the key precursor **14** of epopromycin B starting from (*S*)-*N*-Fmoc-leucinal (***S*-6**) in six steps in 29% overall yield. The present methodology should be applicable to the synthesis of the biologically interesting compounds related to epopromycin B.

Acknowledgements

This study received financial support from Uehara Memorial Foundation and Japan Society for the Promotion of Science (Grant-in Aid for Encouragement of Young Scientists).



Scheme 4.

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