Total Syntheses of Depsipeptide Elastase Inhibitors YM-47141 and YM-47142 with use of Ylide Protection and Coupling Methods

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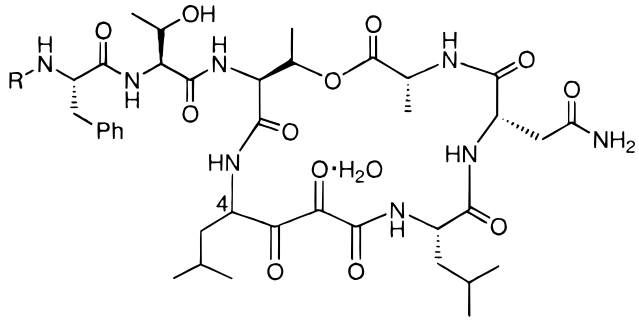
Interest in molecules containing the vicinal tricarbonyl system has been heightened in recent years with the discovery of the potent immunosuppressant activity of the macrolide lactones FK-506 and rapamycin.[1,2] Both of these substances incorporate the tricarbonyl system in the form of intramolecular hemiketals. Elegant total syntheses of these metabolites have been reported[3] along with extensive studies directed at the formation of substructural units considered to be of importance in connection with the biological activity of the natural products.[4]

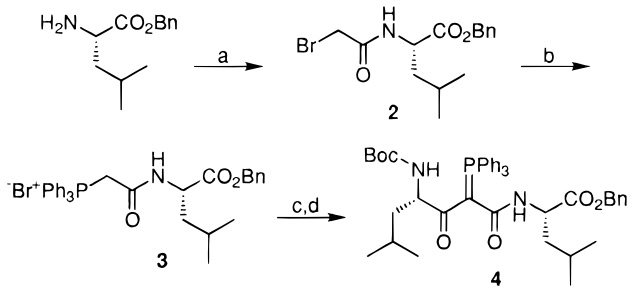
Very recently, two novel elastase inhibitors isolated from *Flexibacter sp*. Q 17897 have been characterized as the depsipeptides YM-47141 (**1a**) and YM-47142 (**1b**).[5] The structures, elucidated by MS and NMR spectroscopic analysis, are noteworthy in that they contain the vicinal tricarbonyl aggregate in the form of hydrated α,*β*-diketo amides. The stereochemistry at C-4 of the unnatural amino acid 2,3-dioxo-4-amino-6-methylheptanoic acid (Dah) was not determined.



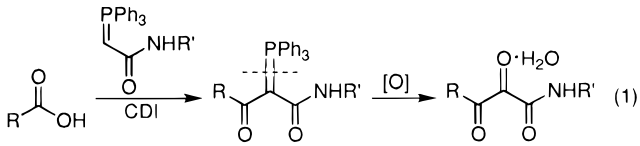
1a, (R=$COCH_2Ph$) YM-47141
1b, (R=$COCH_2CH(CH_3)_2$) YM-47142

We now report the total syntheses of these macrocyclic tricarbonyl depsipeptides, the first examples of hydrated vicinal tricarbonyls in a natural product. This work establishes the stereochemistry at C-4 as that derived from L-leucine, and demonstrates the generality of the phosphoranylidene ylide activation and protection methodology that we have employed in earlier syntheses of α-keto amides.[6−8] The advantages of this procedure (eq 1) are the facile coupling of carboxylic acids with phosphoranes to form stable ylide intermediates which contain highly electrophilic carbonyl groups in protected form. The tricarbonyl units may then be easily unmasked by oxidative cleavage of the carbon phosphorus double bond, affording pure products in high yields.

Scheme 1[a]



[a]Reagents and Conditions: (a) $BrCH_2CO_2H$, DCC, DMAP (92%). (b) PPh_3, THF (97%). (c) Et_3N, CH_2Cl_2. (d) N-Boc-L-Leu-OH, CDI, CH_2Cl_2 (96%, 2 steps).



(1)

An important element in planning our synthesis involved the initial formation of the ylide fragment (**4**) containing the Dah residue with the central carbonyl group of the vicinal tricarbonyl protected in ylide form. We were confident that this unit would be stable under the varied deprotection conditions employed in the elaboration of the depsipeptide. Because of the strongly electrophilic activity of the central carbonyl which predisposes the aggregate to cleavage reactions[9] or benzilic acid type rearrangements,[10] we deferred the deprotection of this group until the last step in the sequence.

We began the synthesis by coupling L-leucine benzyl ester with bromoacetic acid to form **2**, which was then converted to the phosphonium salt **3** and then to the ylide **4** by sequential treatment

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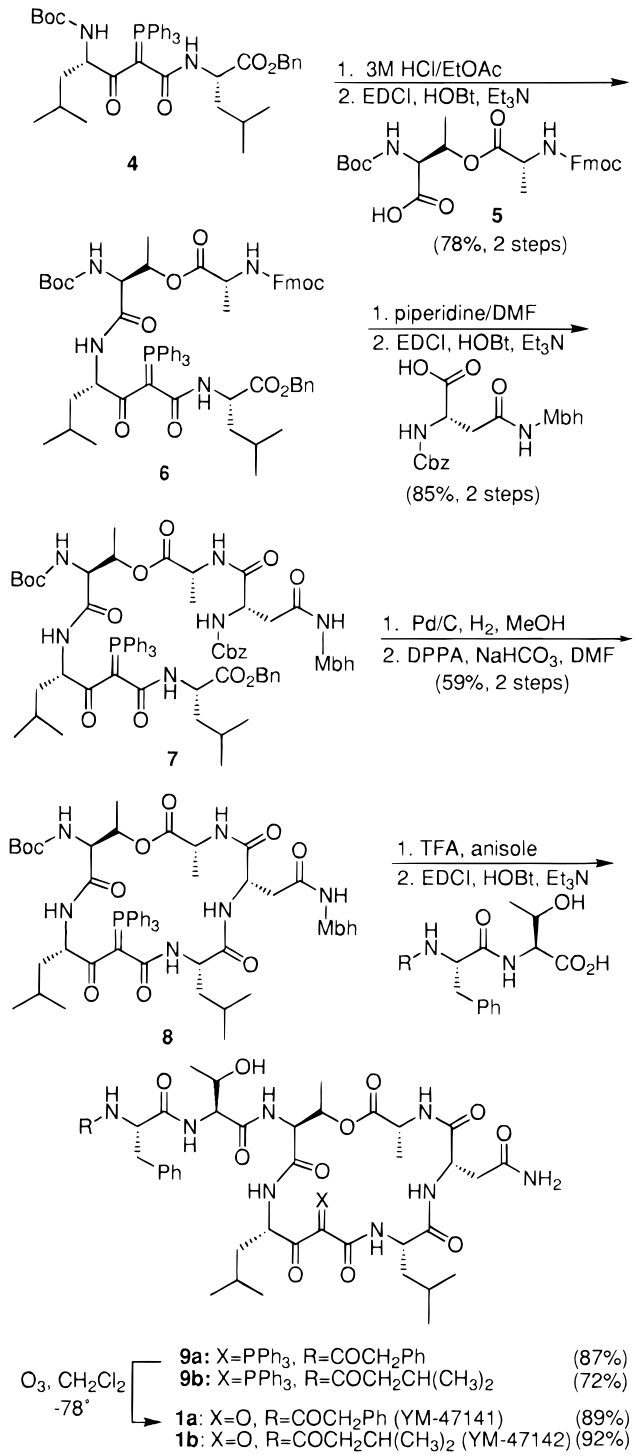
Scheme 2



with Et_3N followed by reaction with *N*-Boc-L-leucine (Scheme 1). In the further progression to the 18-membered ring, we chose to introduce the remaining threonine, alanine, and aspargine residues by the 2+2+1 approach leading to **7** as shown in Scheme 2.

Depsipeptide **5**, derived from L-threonine and D-alanine, was allowed to react (EDCI) with the free amine resulting from HCl removal of the Boc group from **4**, yielding **6**. Removal of the Fmoc group of **6** with piperidine was followed by coupling (EDCI) with N-Cbz asparagine, the primary amido group of which was protected as the 4,4′-dimethoxybenzhydryl (Mbh) derivative.[11] The differentially protected product **7** containing five amino acids was then cyclized to the depsipeptide precursor (**8**), after Pd/C hydrogenolysis of the Cbz and Bn groups, by treatment with DPPA/$NaHCO_3$ in dilute DMF. Installation of each side chain was accomplished by TFA deprotection of both Boc and Mbh groups followed by EDCI coupling with the substituted phenylalanyl threonine to form **9a** (R = $COCH_2Ph$) or **9b** (R = $COCH_2CH(CH_3)_2$).

The resulting macrocyclic ylides **9a** and **9b** represent precursors which could easily be converted to the desired natural products by oxidative cleavage of the carbon−phosphorus double bonds.[12] The final conversion of **9a**,**b** to **1a**,**b** under the mild conditions of ozonolysis (−78 °C, 2 min) took place without complication, forming the natural products in excellent yields (89 and 92%, respectively). The only side product, Ph_3PO, was easily removed by CH_2Cl_2 washing. The ^1H and ^{13}C NMR spectra of both synthetic products YM-47141 and YM-47142 were identical in every respect with the corresponding spectra of the natural products. Since L-leucine was used in the preparation of the Dah fragment, we assign the corresponding L-leucine configuration to the C-4 chiral center. There was no evidence of any epimerization of this center in our synthetic product.[13]

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Supporting Information Available: Experimental procedures for preparation of all compounds in Schemes 1 and 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) We were mindful of possible side reactions in this last step: sensitivity of the primary amide group and secondary alcohol group toward oxidation, β-elimination of the free threonine hydroxyl in the conversion of **9** to **1**. These concerns were allayed by model studies of primary amide units and threonine residues in small peptides, which were stable to the conditions of low-temperature ozonolysis.

(13) The ^1H NMR peaks corresponding to the methine and methylene protons at the γ and δ positions of Dah were indistinguishable from the corresponding absorptions in the natural products. There were no additional peaks in the synthetic product to indicate any epimerization.