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Observation of a new dimeric amino acid derivative in the reaction of methyl *N*-BOC-(*S*)-(3-fluorophenyl)alanate with DIBAL-H and lithio ethyl propiolate

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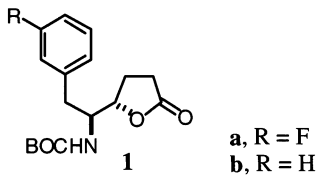
Abstract—A novel amino acid dimer **9a** was isolated while trying to apply a known reduction/nucleophilic addition sequence. This dimer provided information both on the mechanism of the process and on the dependence of the desired reaction on the stoichiometry of reagents. © 2001 Elsevier Science Ltd. All rights reserved.

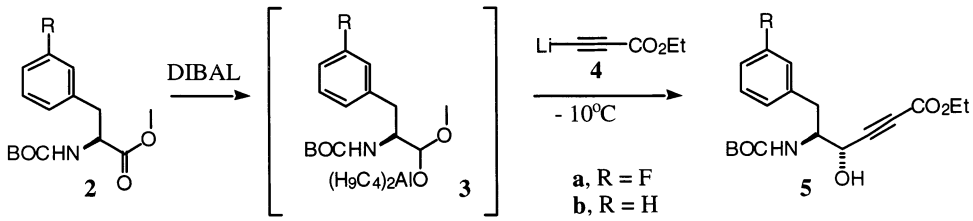
1. Introduction

Recently, we were examining the multikilogram preparation of (*S*,*S*)-lactone **1a**. The des-fluorinated analogue **1b** and various other homologues have been prepared by a number of different syntheses.[1] After reviewing these, it was decided to apply a variation of the route described by Kleinman involving addition of lithio ethyl propiolate **4** to an amino acid aldehyde.[2] The possibility of racemisation of the isolated BOC-3-fluorophenylalanine-derived aldehyde and the moderate selectivities found in the addition of lithio ethyl propiolate **4** to this aldehyde caused us to explore a one-pot procedure shown in Scheme 1.[3] In this reaction, methyl BOC-(3-fluorophenyl)alanate **2a** was reduced with DIBAL-H to aluminoxy acetal **3a** followed by addition of lithio ethyl propiolate **4**. In the course of this work, a novel side reaction was found that was dependent on the stoichiometry of the lithio ethyl propiolate and resulted in the isolation of the novel diol dimer **9a** structurally related to building blocks of HIV protease inhibitors.[4]



2. Results and discussion

In the one-pot reduction/organometallic addition process described in the literature, a slight excess of DIBAL-H was added to the ester. It was found that adding DIBAL-H (1.2–1.5 equivalents) to ester **2a** in THF at −78°C, followed by quenching with acetic acid always resulted in a mixture of aldehyde, starting ester, and alcohol from over reduction. The use of 2.1 equivalents of reductant completely removed the starting ester, yet afforded substantial amounts of alcohol (up to 20%). The optimal conversion was obtained by reversing the order of addition; adding ester **2a** to DIBAL-H in THF at −78°C gave complete consump-



Scheme 1.

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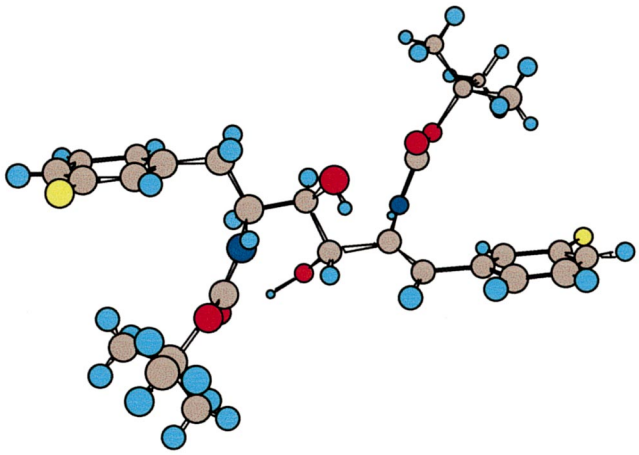


Figure 1. ChemDraw 3D drawing of the single crystal X-ray structure of diol **9a**.

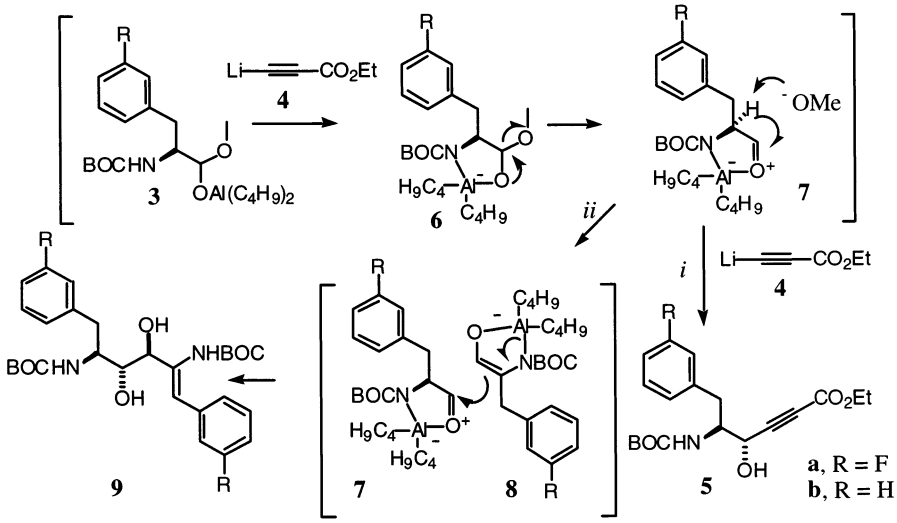
tion of ester and <10% alcohol. During DIBAL-H addition to the ester **2a**, free aldehyde is released from **3a** and undergoes further reduction to alcohol.

The reduction of **2a** to aluminoxy acetal **3a** was carried out with DIBAL-H at −78°C and the cold solution was combined with 1.5 equivalents of **4** at a temperature below −60°C. While the reaction of lithium propiolate **4** with free aldehyde occurs at −78°C, addition of **4** affords product **5** only at >−10°C indicating the absence of aldehyde.[5] The crude reaction mixture looked fairly clean by TLC, but was complex by NMR. A crystalline solid having the same R_f on TLC as the desired **5a** was isolated in up to 20% yield by treating the crude oil with isopropyl ether. This was found to be the novel dimer **9a** by single crystal X-ray analysis[6] (Fig. 1). While the dimerisation of aldehydes or amino acid derivatives in the presence of transition metals is known, the absence of any transition metal and the unprecedented unsaturation in one of the amino alcohol moieties made **9a** an unusual product.

The one-pot, DIBAL-H/lithium propiolate procedure had been performed at Pfizer with phenylalanine analogue **2b** and had produced alcohol **5b** in moderate yield with no mention of major side products. In our hands, the same DIBAL-H/lithium propiolate procedure was repeated with BOC-phenylalanine methyl ester **2b**, and the corresponding diol **9b** was isolated by chromatography of the crude reaction mixture. Therefore, the problems of reproducing the process were unrelated to the presence of a fluorine atom.

To optimise the desired process, the impact of the stoichiometry of **4** was evaluated. One equivalent of propiolate **4** gave little or no **5a** or **9a**. Two equivalents of propiolate **4** gave a reaction mixture which displayed no vinyl resonances in the ^{1}H NMR spectrum, and afforded an HPLC assay consistent with a 6.5:1 mixture of (*S*,*S*)-**5a** and its (*R*)-hydroxyl diastereomer. The reaction was repeated on an 18 mmol scale and the crude **5a** was hydrogenated and cyclised to lactone **1a**. After column chromatography, a mixture representing a 38% yield of the desired (*S*,*S*)-**1a** lactone with 10% of the (*S*,*R*)-diastereomer at the oxygenated centre was isolated. This procedure was also carried out on >10 kilogram scale of **2a** with identical results.

A mechanism for the formation of dimer **9a** is suggested in Scheme 2. The key point is that the initial reduction product **3a** was not fully deprotonated at the BOC-NH, as described above. With 1.5 equivalents of lithio propiolate **4**, the deprotonation and formation of a cyclic aluminate complex **6a** is completed with **4** as a base. Upon warming the reaction, methoxide is lost to give the oxonium species **7a**, and reaction with lithio propiolate provides the desired alcohol **5a** (pathway *i*). If intermediate **7a** is not trapped by a nucleophile such as **4**, a second deprotonation from the α-carbon centre of **7a** provides a nucleophilic species **8a** that reacts with oxonium **7a** (pathway *ii*). Another possibility is that the methoxy group is displaced by lithio propiolate directly in pathway *i* or is eliminated as methoxide to generate intermediate **8a**. In literature examples of this



Scheme 2.

reaction, a large excess of the organometallic reagent, typically 3 equivalents, were used. The cyclic aluminate complex provides a rationale for the relationship between the stoichiometry of lithio propiolate **4** and the improved diastereomeric ratio of alcohol **5a** over its diastereomer as compared with direct addition to the free aldehyde. This also explains the higher reaction temperature and the origin of the double bond in **9a**. Pinacol **9a** was isolated as a single enantiomer.

3. Conclusion

Altering the stoichiometry of the reagents in a known synthetic procedure resulted in the formation of a novel dimer **9a** and provided some insight into the mechanism of the transformation.[7]

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5. When isolated aldehyde was treated with excess lithio ethyl propiolate **4** at −78°C, reaction occurred without warming and the desired **5a** and its diastereomer were isolated in a 3:1 ratio and 60% yield.
6. *trans*-2-(5*S*)-Bis-(*tert*-butoxycarbonylamino)-1,6-bis-(3-fluorophenyl)-(3*S*,4*R*)-dihydroxy-hex-1-ene **9a**: Methyl *N*-BOC-(*S*)-(3-fluorophenyl)alaninate **2a** (10.8 g, 36.3 mmol) in dry toluene (50 mL) was cooled to −78°C under nitrogen and treated with DIBAL-H (1.5 M in toluene, 49.6 mL, 74.4 mmol) dropwise over 40 min and the mixture was stirred at low temperature for 0.5 h. In a separate flask, ethyl propiolate (5.5 mL, 54.3 mmol) was added dropwise at −78°C to lithium hexamethyldisilazane in tetrahydrofuran (1 M solution, 54.3 mL, 54.3 mmol) over 20 min. The toluene solution was transferred to the lithio propiolate solution by means of a cannula over 2 min and the reaction was allowed to warm to room temperature and stirred overnight. The reaction was recooled to −10°C and acetic acid (13 mL) was added dropwise over 20 min. The reaction was poured into a mixture of an equal volume (100 mL each) of ethyl acetate and aqueous citric acid (17 g) and this was stirred for 45 min to solubilise the aluminium salts. The organic layer was separated and washed with water (two washes) and brine. The solvent was evaporated in vacuo and the crude oil was stirred with isopropyl ether to provide a first crop of diol **9a** (0.9 g). Further material was recovered after chromatography over silica gel with 10% ethyl acetate in methylene chloride. Mp 191–193°C (dec.). $[\alpha]_D$ −40.6 ($c=0.88$, MeOH). NMR ($CDCl_3$) δ 7.27–6.85 (m, 8), 6.85 (s, 1), 5.97 (bs, 1), 4.90 (d, 1), 4.43 (d, 1), 4.15 (m, 1), 3.93 (m, 1), 3.65 (bs, 1), 3.32 (m, 1), 2.95 (d, 2), 1.43 (s, 9), 1.32 (s, 9). Mass spectrum: m/e 534 (M^+). Anal. calcd for $C_{28}H_{36}F_2N_2O_6$: C, 62.91; H, 6.79; F, 7.11; N, 5.24. Found: C, 62.70; H, 6.72; F, 7.28; N, 5.16%.
7. For an additional discussion of this type of process see: Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469–5480 and references cited therein.