Pergamon

Tetrahedron Letters, Vol. 36, No. 14, pp. 2505-2508, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00255-3

Synthesis of a Novel C_2-Symmetrical (2S,5S)-2,5-Bis-[(1,1-dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene : Applications in the Synthesis of Potential HIV Protease Inhibitors

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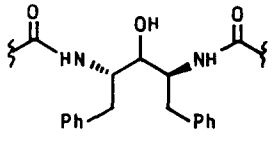
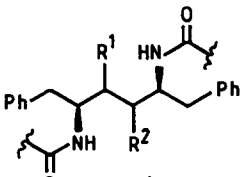
Abstract : The synthesis of a novel and versatile (2S,5S)-2,5-bis-[(1,1'-dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene (**2**) based on Julia's olefination strategy coupled with its application in stereoselective preparations of HIV protease inhibitors has been discussed.

The vogue of synthesising HIV protease (PR) inhibitors that can antagonise HIV progression and serve as specific anti-AIDS agents, has intensified[1]. Complexes derived from HIV PR/inhibitors interactions have been studied by X-ray crystallography and several new structures identified[2]. Protease inhibitors (**1**) containing a C_2-axis of symmetry are the most favoured targets because axes of symmetry of both inhibitor and enzyme could coalign during their interactions[3]. The pseudosymmetrical deoxygenated inhibitors (**1b**) that lack one hydroxyl group also show pronounced activity[4]. As a part of our collaborative developmental programme on



1a

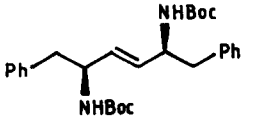


1b

$R^1 = R^2 = OH$

$R^1 = OH, R^2 = H$

HIV-protease inhibitors we have undertaken investigations to design new structures in this domain and also improve methodologies for existing structures. We now describe the first synthesis of a unique C_2-symmetrical compound as a potential protease inhibitor-(2S,5S)-2,5-bis-[(1,1-dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene (**2**) and demonstrate its versatility in the stereoselective synthesis of known and unknown analogues.

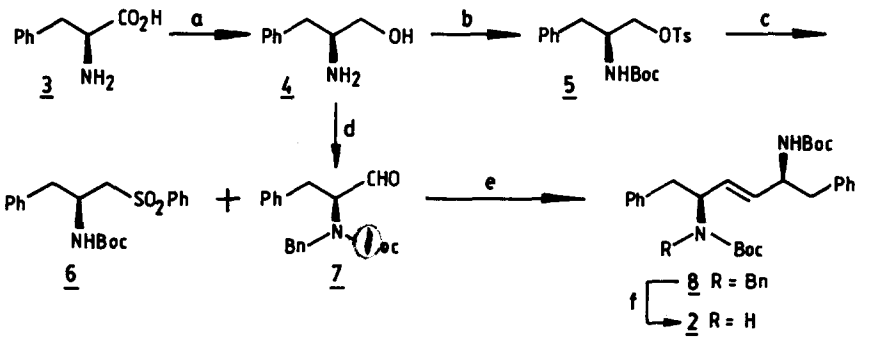


2

Based on Julia's olefination strategy as a key step[5], a route to **2** was envisaged with L-phenylalanine (**3**) as the starting point. Reduction of **3**[6] in presence of $NaBH_4$-I_2 in refluxing

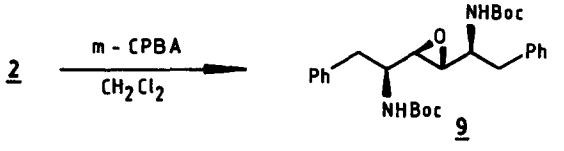
THF gave L-phenylalanol (4). After protecting the NH_2 group with Boc, it was treated with p-toluenesulfonyl chloride-pyridine to afford the tosylate derivative (5). Subsequent displacement of the tosyl group with sodium thiophenolate in MeOH/THF at RT followed by oxidation with MCPBA in CH_2Cl_2 afforded the requisite sulfone derivative 6.

Scheme

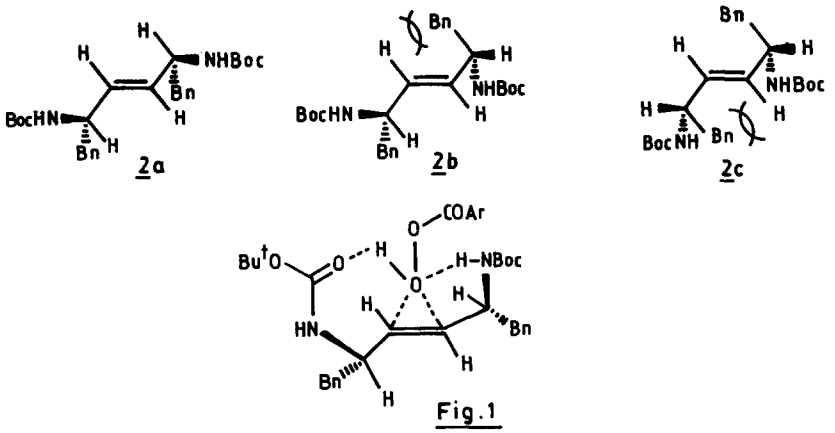


a) $NaBH_4/I_2$, THF, 18 h, Δ; b) (i) $(Boc)_2O$, THF:H_2O, 1h, RT, 95%; (ii) TsCl, Py, CH_2Cl_2, 12 h, RT, 90%; c) (i) NaSPh, MeOH:THF, 3 h, RT, 83%; (ii) MCPBA, CH_2Cl_2, 1 h, RT, 95%; d) (i) PhCHO, $NaBH_4$, MeOH, 3-4 h, RT, 77%; (ii) $(Boc)_2O$, THF:H_2O, 1 h, RT, 95%; (iii) SO_3-Py, Et_3N, DMSO, 0°-RT, 1 h; e) (i) n-BuLi, THF, -78°C, 1 h; (ii) Ac_2O, Py, CH_2Cl_2, 12 h, RT; (iii) 6% Na-Hg, Na_2HPO_4, MeOH, 12 h, RT; f) Na/liq. NH_3, THF, -33°C, 37% overall.

In an another sequence, compound 4 was transformed into 7 in three high yielding steps. For instance, 4 was benzylated with a mixture of PhCHO-$NaBH_4$ in methanol, the NHBn group was protected with $(Boc)_2O$ and the CH_2OH group oxidised with SO_3:Py in DMSO to afford the aldehyde 7. The coupling reaction between 6 and 7 was achieved by using 2 equivalents of n-BuLi at -78° in THF. The resulting β-hydroxysulfone intermediate was not fully characterised but successively treated with acetic anhydride-pyridine, and 6% Na-Hg in presence of Na_2HPO_4 buffer in MeOH for 12 hrs to afford **8** (overall yield of 37%). Removal of benzyl group from **8** was effected with Na/liq. NH_3 at -33° to provide 2, m.p. 133°, $[\alpha]_D$-14° (c 1, $CHCl_3$).



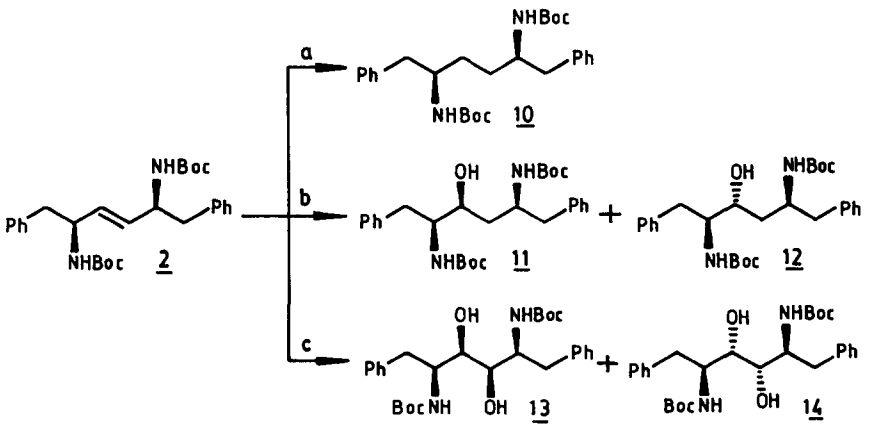
Compound 2 was treated with 3 equivalents of MCPBA in CH_2Cl_2 at ambient temperature to provide the epoxide derivative 9 { $[\alpha]_D$ +25° (c 0.3, $CHCl_3$) } almost as an exclusive diastereomer (33:1, HPLC). The high degree of threo-selectivity[7] has been explained by taking into account the conformations **2a-c**. The cooperative coordination[7,8] of peracid by carbamates of the preferred conformer **2a** influenced the β-attack as delineated in Figure 1. The structure of the epoxide **9** was supported by spectral data.



The reduced product **10** (dideoxygenated inhibitor analogue) was conveniently produced in almost quantitative yield by hydrogenation over 10% Pd-C in methanol at 45 psi. The C_2-symmetrical structure of **10** was evident from the ^{1}H-NMR spectrum.

We next studied the hydroboration-oxidation of **2**. Hydroboration of **2** with 2M solution of BH_3:Me_2S complex in THF at 0°-RT followed by oxidation with alkaline H_2O_2 gave a 4:1 mixture of diastereomeric products (**11** and **12**). Separation by silica gel chromatography gave enantiomerically pure compounds whose physical and spectral properties were identical with authentic values[9], thus confirming these structures beyond any doubt.

There is a current renaissance in the series of HIV protease inhibitors containing diamino diol core unit (**1a**) in which the C_2 axis bifurcates the carbons bearing hydroxyl groups. Fortunately all the three diol diastereomers are sufficiently active[3]. We believe that C_2 symmetrical **2** could be exploited for the preparation of R,R- and S,S- inhibitors by making use of catalytic osmylation process. The straightforward catalytic osmylation of **2** with OsO_4-NMO in t-BuOH-H_2O mixture at room temperature provided a mixture of diol **13** and **14**, albeit with



a) 10% Pd-C, MeOH, 45 psi, 12 h, 97%; b) BH_3-Me_2S, NaOH, H_2O_2, THF, 4 h, 0°-RT, 85%; c) OsO_4, NMO, t-BuOH:H_2O (1:1), 12 h, RT, 90%.

only moderate diastereofacialselectivity (2:3)[10]. However, both the diols were separated by column chromatography on silica gel and their structures (**13** and **14**) were deduced by comparision of spectral data. In one experiment, the asymmetric dihydroxylation of **2** with AD-mix-α in t-BuOH-water at 0°-RT gave 1:4 mixture of **13** and **14** (HPLC)[11]. Further efforts in dihydroxylation of **2** are currently underway in these laboratories[12].

This manuscript clearly manifests that (2S,5S)-1,5-bis[(1,1-dimethylethoxy)carbonylamino]-1,6-diphenylhex-3-ene (**2**) is indeed a novel building block in the synthesis of series of potential HIV protease inhibitors. The above methodology also offers a unique opportunity to produce a new class of protease inhibitors harbouring different aryl substituents at the ends, by simply varying amino acid precursors. This study is currently under progress.

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12. Spectral data of some selected compounds : **2** : ^{1}H NMR (200 MHz, $CDCl_3$): δ1.40 (s, 18H), 2.74 (br, 4H), 4.32 (br, 4H), 5.42 (br, 2H), 7.0-7.3 (m, 10H), CI-MS : 467 (M^+1); **9** : ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 18H), 2.65-2.95 (m, 6H), 3.91 (br, 2H), 4.38 (d, 2H, J=9.6 Hz), 7.1-7.3 (m, 10H); **10** : ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2-1.6 (m, 4H), 1.38 (s, 18H), 2.72 (bd, 4H), 3.75 (br, 2H), 4.18 (d, 2H, J=9.0 Hz), 7.0-7.35 (m, 10H), CI-MS : 469 (M^++1).

IICT Communication No. 3497

(*Received in UK* 17 *January* 1995; *accepted* 3 *February* 1995)