HIV Protease Inhibitors Part 2: [3+2] Cycloaddition, Isomerization; and Ring Expansion en route to 4,5-Substituted Cyclohexenones

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Abstract: 4,5-Substituted cyclohexanone **10** and its derivatives are carbocyclic analogues of Indinavir **3** and are expected to have antiviral activity. Early attempts to obtain these compounds via a diastereoselective [3+2] cycloaddition between **19** and **14** failed due to the sensitivity of the cycloadduct **24**. It proved possible to obtain **30** from the α,β-unsaturated ester **27**: [3+2] cycloaddition, isomerization, and ring expansion provided α,β-unsaturated ketone **31** from ester **26** in good yields. Further transformations of **31** gave the hydroxyethylamino inhibitor analogues of Indinavir **3**.

Key words:: [3+2] cycloaddition, cyclopentene, ring expansion, cyclohexenone, HIV protease inhibitor

In the preceding paper[2] we have described a route to 4-substituted carbocyclic Phe-Pro mimetics **1** using diastereoselective Diels–Alder reactions. We also hoped to develop a route to 5-substituted compounds **2** since molecular modelling, as well as marketed HIV protease inhibitors such as Indinavir **3**, indicate that substituents at this position should be tolerated and may have important effects on potency and pharmacokinetic properties (Figure 1).

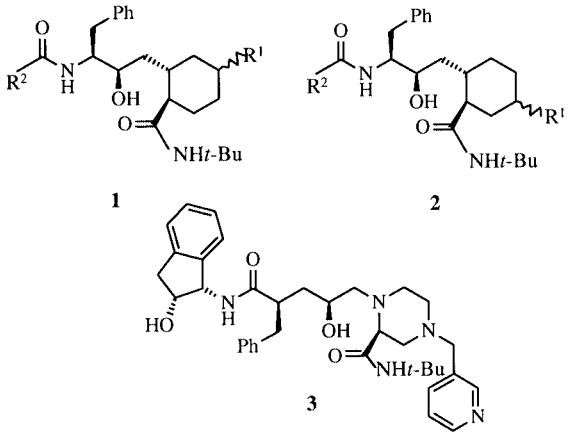


Figure 1

Attempts to prepare 5-functionalized carbocycles using Diels–Alder chemistry were not successful. The dienophile **4** (Scheme 1) did not react with dienes **5**[3] or **6**[4] under either thermal conditions or Lewis acid catalysis to give the α-functionalized ketone **7**; instead only the starting materials were recovered (Figure 2).

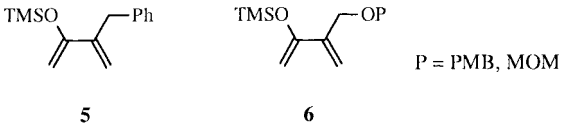
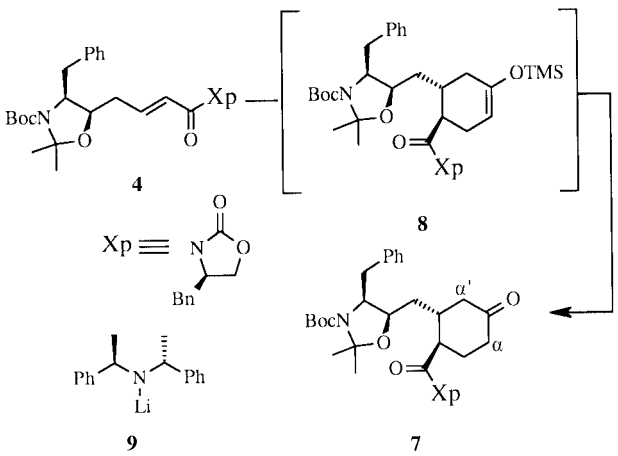


Figure 2

It proved difficult to oxidize in situ the silyl enol ether **8**[5] formed by reaction of **4** with 2-(trimethylsilyloxy)-1,3-butadiene, whilst use of Danishefsky's diene under similar conditions lead only to decomposition. Attempts to effect conversion of **7** to **8** using chiral amide[6] bases such as **9**[7] were also unsuccessful (Scheme 1).



Scheme 1

We decided then to modify our strategy and to access ketone **10** by ring expansion. Ozonolysis of cyclopentene **11** followed by crotonization of the intermediate keto-aldehyde should lead, after epimerization of the carbon α to the ester, to the more stable *trans*-isomer **10** (Scheme 2). It was hoped that **11** could be obtained from **12**, after isomerization of the double bond and reduction of the subsequent vinyl sulfone. **12** would result from reaction of allylic sulfone **14**[8] with lactone **13**.

We chose as our starting material the epoxide **15**,[9] for which a large-scale synthesis was already known (Scheme 3). Attempts to react **15** with methyl propionate under Yamaguchi's conditions[10] gave the acetylene **17** together with substantial amounts of the ketene **18**[11] (as a

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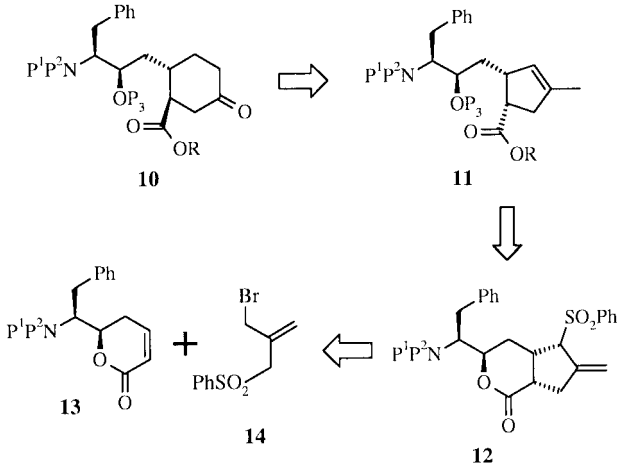
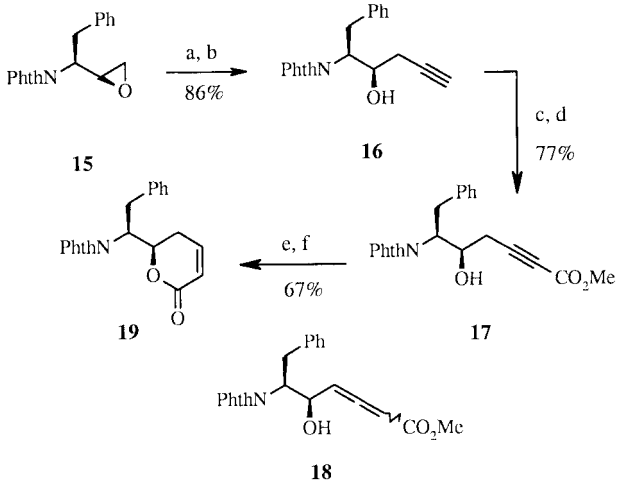


Scheme 2 Retrosynthetic analysis.



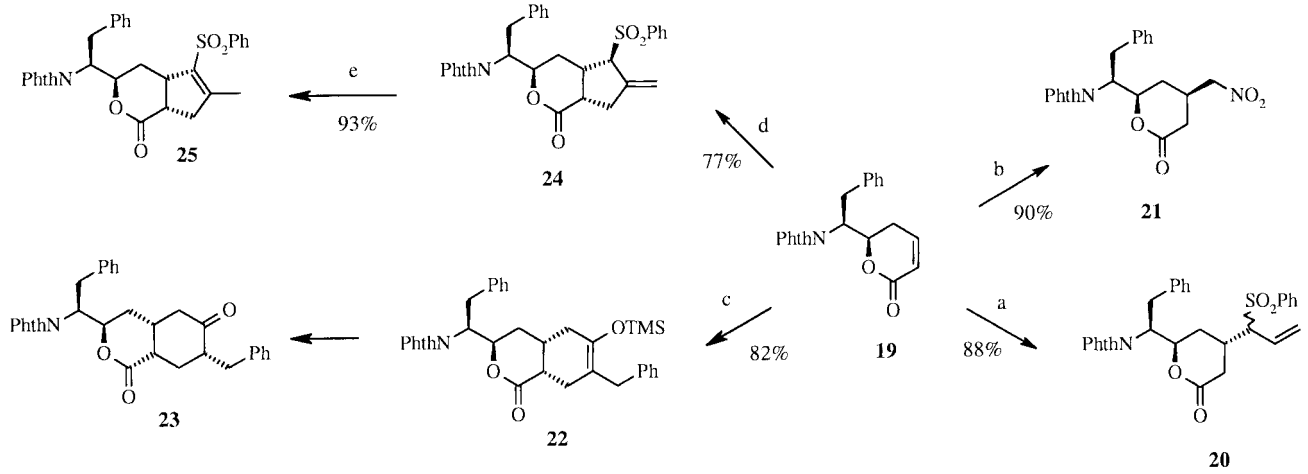
Scheme 3 Conditions: a) TMSCCH, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, –78 °C. b)TBAF, THF, 0 °C. c)TMSCl, Et_3N, THF, r.t. d) LDA, $ClCO_2Et$, THF, –78 °C to r.t.; HCl 1 N. e) H_2, Lindlar's catalyst, EtOAc. f) PTSA, $PhCH_3$, Dean–Stark, reflux.

2:1 mixture of isomers), from which the acetylene was difficult to separate. We decided then to synthesise **17** via functionalization of alkyne **16**. Reduction of **17** using Lindlar's catalyst followed by lactonization[12] gave **19**[13] in good overall yield.

Lactone **19** reacts kinetically with the anions of allylic sulfones to give stereoselectively compounds such as **20**, whilst addition of nitromethane[14] gives only the thermodynamically favoured *cis*-isomer **21** (Scheme 4). On the other hand, addition of azide[15] affords a 1:1 mixture of isomers. Diels–Alder reaction of **19** and **7** was found to be stereoselective and gave, after acidic workup, bicyclic adduct **23**, presumably due to kinetic protonation of the concave enol ether ether **22**. Interestingly, this reaction can be considered, in addition to hydrogenation, as a way to access highly functionalized all-*cis* cyclohexanes, in which one of the alkyl chains is in the thermodynamically unfavored pseudo-axial position.

Reaction of **19** with sulfone **14** was also stereoselective and gave **24** as a single isomer whose stereochemistry was determined by X-ray crystallography (Figure 3).[16]

The 6-membered lactone adopts a highly strained boat conformation. Treatment of **24** with potassium *tert*-butoxide gave vinyl sulfone **25** in 93% yield. Reduction of sulfone **25** proved difficult and lead to decomposition, mainly because of the strain of the bicyclic structure. We showed, for example, that treatment of **24** with samarium iodide gave the corresponding lactol in 70% yield, releasing the strain of the boat conformation of the starting material.[17] Unfortunately, all attempts to saponify lactones **24** or **25** gave prior or concomitant opening of the phthalimide group. Attempts to remove the phthalimide group in order to replace it by a more robust protecting group, even using very mild conditions,[18] were unsuccessful.



Scheme 4 Conditions: a) allyl sulfone (1.2 equiv), LDA, THF, –78 °C. b)CH_3NO_2, DBU, r.t. c) 7 (3 equiv), Et_2AlCl (3 equiv), THF, r.t. d) **14** (1.2 equiv), LDA, THF, –78 °C. e) *t*-BuOK, *t*-BuOH–THF, 0 °C.

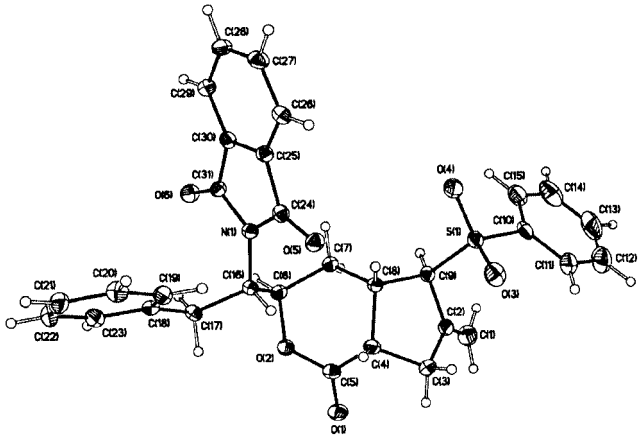


Figure 3 ORTEP diagram of compound 24.

The length of the synthesis of **19**[19] together with the problem of the choice of a good protecting group[20] for the side chain nitrogen led us to move towards a shorter approach using **27** as a Michael acceptor (Scheme 5).

Treatment of **27** with the lithium salt of sulfone **14** gave, in high yield[21] **28**, which was isomerized to **29** prior to reduction.[22] Ozonolysis of **30** followed by aldolization-elimination provided the desired ketone **31** in good yield. Ketone **31** was then easily transformed to **32** by reduction of the double bond, saponification and coupling to *tert*-butyl amine. The transformations previously described[2] on the isomeric 4-ketone were also applicable to **32**: for example, reduction of **32** using Luche's[23] conditions followed by methylation gave ether **33** in good yields and with high diastereoselectivity.

We have thus developed efficient syntheses of both structures of both 4- and 5-substituted carbocyclic mimetics of scissile Phe-Pro. The biological activities of HIV protease inhibitors derived from these intermediates will be reported in due course.

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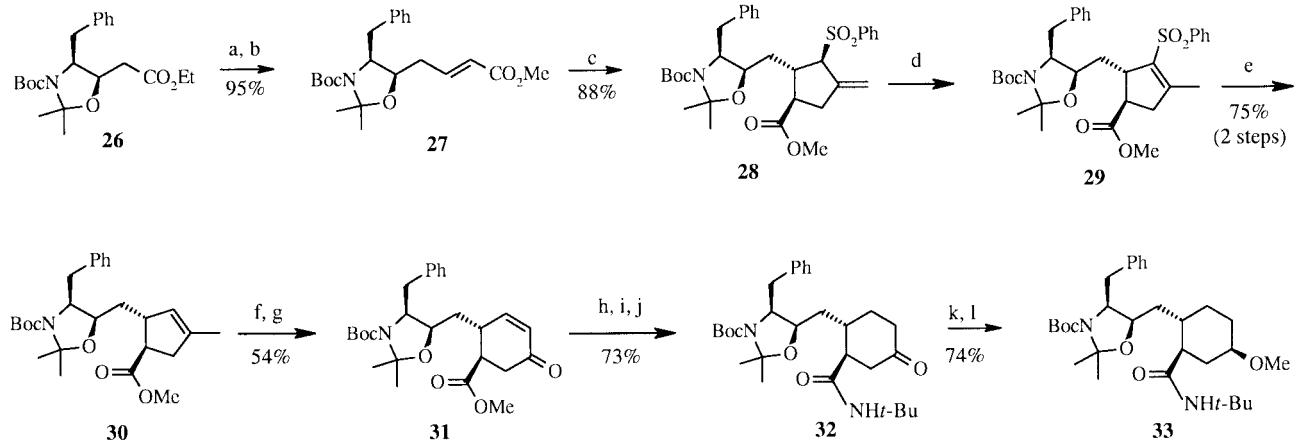

Scheme 5 Conditions: a) DIBAL-H, $PhCH_3$, –78 °C. b) $Ph_3PCHCO_2CH_3$, THF, r.t. c) 15 (1.2 equiv), LDA, THF, –78 °C. d) MeONa, MeOH, 0 °C. e) Na/Hg 5%, MeOH, KH_2PO_4, 0 °C. f) O_3, MeOH–CH_2Cl_2, –78 °C; PPh_3, –78 °C to r.t. g) PTSA, $PhCH_3$, Dean–Stark, reflux. h) H_2, Pd/C, EtOAc, RT. i) LiOH, THF–water, 0 °C. j) HOBT, EDAC·HCl, *t*-$BuNH_2$, CH_2Cl_2, 0 °C to r.t. k) $NaBH_4$, $CeCl_3$, MeOH, –10 °C to r.t. (ds> 90/10). j) NaH, DMF, 0 °C; MeI, 0 °C to r.t.

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