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Traceless solid-phase synthesis of hydroxylated cyclopentenones

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ABSTRACT

Intramolecular nitrone–alkene cycloadditions on solid phase can be performed using polymer-bound hydroxylamine. Condensation of this reagent with sugar derived 4-pentenals followed by N–O cleavage, quaternization of the amine thus produced, and finally oxidative elimination of the amino group detaches the chiral hydroxylated cyclopentenones from the polymer. The natural antibiotic pentenomycin I was prepared in this way.

Cyclopentenone (+)-**1** and its enantiomer (Fig. 1) are important chiral building blocks,[1] widely used in organic synthesis.[2] A number of publications describing their enantioselective syntheses have been reported in the literature, including both asymmetric synthesis[3] and chiral pool.[4] In addition, the antibiotic pentenomycin I (**2**),[5] a hydroxymethylated derivative of (+)-**1**, isolated from culture broths of *Streptomyces eurythermus*, is active against both Gram-positive and Gram-negative bacteria. It has attracted considerable attention and a number of racemic and chiral syntheses have been reported.[6]

We have recently reported[7] a methodology for the synthesis of such compounds (Scheme 1). Starting from the appropriate carbohydrate, a γ,δ-unsaturated aldehyde or ketone can be prepared, which upon intramolecular nitrone cycloaddition is converted to aminocyclitols. Quaternization of the latter, followed by oxidative elimination of the amino group, leads to the formation of the desired cyclopentenone.

It was considered at this point that cyclopentenone synthesis would be simplified significantly by transfer of the above methodology from solution to solid phase. Despite the fact that inter- and intramolecular 1,3-dipolar nitrone-olefin cycloadditions have been extensively studied and have found wide application in the synthesis of various natural products and synthetic materials,[8] their application in solid-phase synthesis is limited,[9] particularly when compared to other 1,3-dipoles.[10] To realize this aim, we firstly had to solve two problems: (i) find an efficient linker in order to attach the substrates on the polymer and (ii) to use reagents compatible with the solid-phase synthesis.

We decided to bind the hydroxylamine to the polymer using two similar linkers **13a,b** (Scheme 2). This technique has the advantage of being traceless, since in the last step the formation of an enone detaches the product from the polymer. The first of these two linkers, which in fact has the hydroxylamine attached to the Wang resin has already been used for intermolecular nitrone cycloaddition to alkenes,[9c] catalyzed by Yb(OTf).[3]

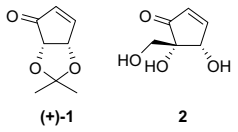
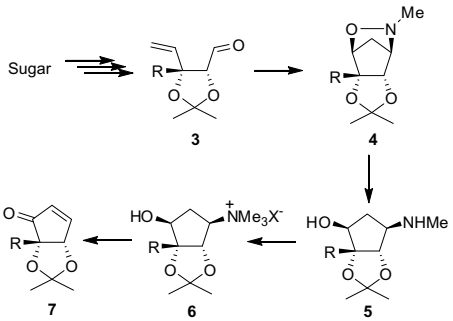


Figure 1. Target cyclopentenones.



Scheme 1. General synthetic scheme towards cyclopentenones.

We, however, attached hydroxylamine to the solid phase using a different approach to that mentioned in the literature. Starting from the Merrifield resin, the 4-hydroxybenzyl alcohol or 1,4-butanediol linkers were introduced by standard procedures, and then the protected hydroxylamine was attached via a Mitsunobu reaction. All modifications were followed by infrared spectroscopy and after removal of the protecting groups, the weight increase of the polymer corresponded to 80% and 95% overall yields for **13a** and **13b**, respectively. In addition, **12a,b** were subjected to a

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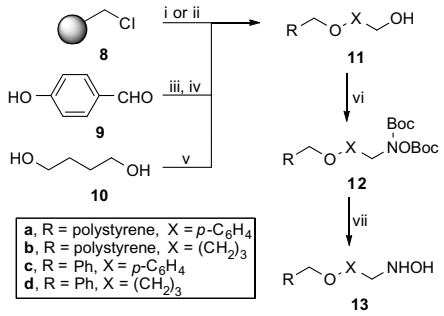


Scheme 2. Reagents and conditions: (i) 4-hydroxybenzaldehyde, NaOH, DMSO, then $NaBH_4$, MeOH, reflux; (ii) 1,4-butanediol, NaH, DMF, 2 h at 0 °C, then **8**, *n*-Bu_4NI, 20 °C, 12 h; (iii) BnCl, NaOH, DMF, 85%; (iv) $NaBH_4$, MeOH, 98%; (v) Ag_2O, BnCl, DCM, 20 °C, 2 h, 98%; (vi) BocNHOBoc, DIAD, Ph_3P, THF, 0→20 °C, 24 h; (vii) TFA, DCM, 1–3 h, then Na_2CO_3.

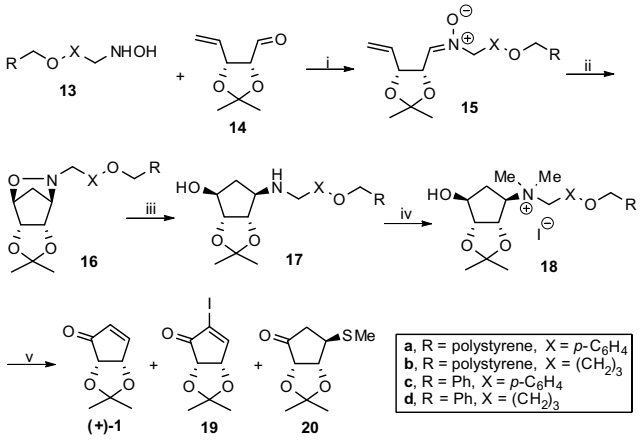
second reaction cycle with BocNHOBoc, but the weight of the polymer remained practically unchanged.

In order to address the problem of checking reaction progress and completion, we prepared N-substituted hydroxylamines **13c,d** (Scheme 2) as models that mimic the monomeric units of the polymer and the linkers used. Their synthesis was achieved easily by preparing the corresponding benzyloxybenzyl alcohol **11c** and *O*-benzyl-1,4-butanediol **11d**, followed by Mitsunobu reaction with BocNHOBoc and subsequent deprotection.[11]

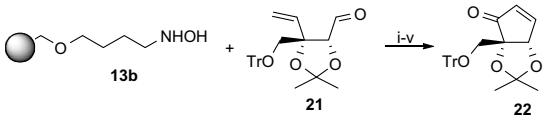
With the model compounds **13c,d** in hand, we were ready to apply the protocol depicted in Scheme 1 for the synthesis of enantiomerically pure hydroxylated cyclopentenones. Condensation of **13c,d** with pentenal **14** led to the formation of nitrones **15c** (69%) and **15d** (77%), which upon heating in refluxing chlorobenzene gave adducts **16c** and **16d** in 74% and 65% yields, respectively (Scheme 3).

The problem we had to face at this point was to use a new reagent in order to cleave the N–O bond, since the heterogenous catalysis used hitherto was not compatible with the solid-phase synthesis. Samarium iodide[12] proved to be an excellent reducing agent and compounds **17c,d** were prepared from **16c,d** in 93% and 94% yields, which were quaternized using MeI and K_2CO_3.

In the final step, a number of conditions were investigated in order to eliminate oxidatively the ammonium group and to detach the products from the polymer. PDC oxidation in CH_2Cl_2 led to the formation of the iodinated product **19**[7] together with the desired



Scheme 3. Reagents and conditions: (i) MeOH, 20 °C, 12 h; (ii) PhCl, reflux, 1–2 h; (iii) SmI_2, THF; (iv) MeI, K_2CO_3, THF, 20 °C, 20 h; (v) $(COCl)_2$, DMSO, Et_3N, DCM, −65 °C (see text also).



Scheme 4. Reagents and conditions: (i) MeOH, 20 °C, 12 h; (ii) PhCl, reflux, 1–2 h; (iii) SmI_2, THF; (iv) MeI, K_2CO_3, THF, 20 °C, 20 h; (v) $(COCl)_2$, DMSO, Et_3N, DCM, −65 °C (see text also).

cyclopentenone (+)-**1** in a 3:1 ratio and 37% combined yield from **18d**. Moffatt oxidation (DCC, DMSO, pyridine, TFA, benzene, 20 °C) of **18d** again gave the same products but in an improved yield and ratio (68%, 1:1). Swern oxidation [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −40 °C] converted the same substrate exclusively to the thiomethyl product **20**. This compound apparently derives from the desired cyclopentenone formed by 1,4-addition of a 'methylthiol' equivalent intermediately generated by reduction of DMSO. Thus, the Swern oxidation at lower temperature (−65 °C) prevented 'methylthiol' addition and afforded the cyclopentenone (+)-**1** as the sole product from both the ammonium salts **18c,d** in very good yields (76% and 79%, respectively).[11,13]

Having established the optimized conditions, the solid-phase synthesis was then performed easily by following the sequence discussed above. Finally, the cyclopentenone (+)-**1** was detached from the polymer by Swern oxidation at −65 °C in 18% and 15% yields based on the loading of the starting resin, respectively, contaminated by a 2% yield of **20**. The overall yields are considered satisfactory, although somewhat lower than that of the solution-phase synthesis (24%).[7a] It is noteworthy that both (+)-**1** and (−)-**1**, which are widely used key intermediates in organic synthesis, can be prepared in this way, since both enantiomers of **14** are readily available, thus increasing the utility of the present method.

The scope of this methodology was further shown by condensing aldehyde **21**[7] with the polymer-bound hydroxylamine **13b** (Scheme 4). Following the five-step sequence described in Scheme 3, protected pentenomycin I **22** was prepared in 16% overall yield, based on the loading of the starting resin.[11,13]

In conclusion, polymer-bound hydroxylamine proved to be a very useful material for intramolecular nitrone–alkene cycloadditions. The methodology in solution phase recently reported by us was transferred successfully to the solid phase and a traceless synthesis of enantiomerically pure cyclopentenones was achieved.

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Supplementary data

Supplementary data (^1H NMR spectra of compounds **12c,d**, **15c,d**, **16c,d** and **17c,d**, and ^{13}C NMR spectra of compounds **12c,d**, **15d, 16d**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.080.

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11. All the new compounds isolated, **12c**,**d**, **15c**,**d**, **16c**,**d**, **17c**,**d** and **20**, gave analytical and spectroscopic data consistent with the proposed structures. The known compounds (+)-**1**, **19** and **22** were characterized from their $[\alpha]_D$ values and NMR data, which were identical to those reported in the literature. *Selected data for compound* **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.73 (d, J = 5.3 Hz, 1H), 4.37 (d, J = 5.3 Hz, 1H), 3.42 (d, J = 7.6 Hz, 1H), 3.04 (dd, J = 18.5, 7.6 Hz, 1H), 2.26 (d, J = 18.5 Hz, 1H), 2.19 (s, 3H), 1.42 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.2, 113.0, 80.9, 78.0, 41.9, 39.9, 26.7, 24.9, 14.6. HRMS m/z: calcd for $C_9H_{14}O_3SNa$ [$(M+Na)^+$]: 225.0556; found 225.0553.
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13. The products released from the support were of satisfactory purity ($\geqslant$95%) as determined by ^{1}H NMR.