Tetrahedron Letters 51 (2010) 2160–2163

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Syntheses of structurally diverse amino acids, including δ-hydroxylysine, using the acyl nitroso Diels–Alder reaction

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ARTICLE INFO

Article history:
Received 18 December 2009
Revised 30 January 2010
Accepted 15 February 2010
Available online 18 February 2010

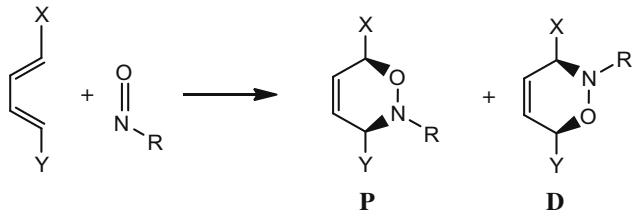
ABSTRACT

By virtue of its ability to introduce amino and hydroxy functionalities in a 1,4-relationship with fully controlled relative stereochemistry, the acyl nitroso Diels–Alder (ANDA) reaction is ideally suited to the synthesis of structurally diverse, including hydroxylated, amino acids. The major issue to be tackled is that of regiochemistry in the ANDA addition to unsymmetrical dienes. The transformation of three diverse types of ANDA adducts into amino acids is described, in particular, the synthesis of δ-hydroxylysine, an important constituent of collagen, as a single (2*SR*, 5*SR*) diastereoisomer in protected form.

The nitroso Diels–Alder reaction was described by Wichterle in 1947[1] and has been frequently employed by synthetic chemists in pursuit of a wide variety of structures. An especially attractive feature of this reaction is that it introduces nitrogen and oxygen substituents in a single step with a complete control of relative 1,4-stereochemistry. With appropriate substitution in the diene employed, therefore, the reaction should be ideally suited to the synthesis of hydroxy amino acids (and other amino acids) as single diastereoisomers.

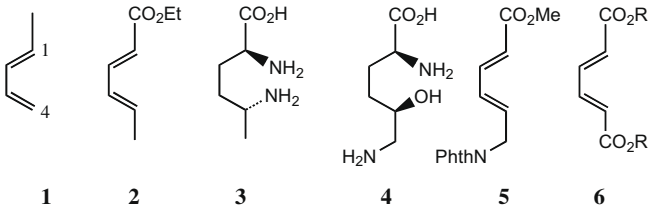
For an unsymmetrical diene, two products are possible (Scheme 1), termed 'proximal (**P**)' and 'distal (**D**)' by Boger,[2] according to the disposition of the O atom with respect to the side-chain (X or Y) of highest atomic number. From a synthetic point of view, the reactivity of the nitroso group is maximised by attachment to strongly electron-withdrawing groups, particularly via sp^2 centres, for example, acyl groups. Henceforth this variant will be referred to as the acyl nitroso Diels–Alder (ANDA) reaction. In particular, the benzyloxycarbonyl and *t*-butoxycarbonyl nitroso dienophiles (ZN=O and BocN=O),[3] readily prepared in situ by oxidation of the corresponding hydroxylamines, are of great value because they combine high reactivity with mild conditions required to release the free amine later.

The predictability of obtaining **P** or **D** adducts is clearly paramount for synthesis. A seminal theoretical study by Leach and Houk[4] showed that frontier orbital considerations are most significant. For any 1-substituted diene **1**, the highest HOMO coefficient will be located at C(4): hence the nitroso N bonds to this position. When substituents X and Y (Scheme 1) are close in their electronic character, a **P**/**D** mixture is predicted and the authors[4] commented: 'a delicate balance of electronic and steric factors will affect the result'.



Scheme 1. Proximal (**P**) and distal (**D**) nitroso adducts from an unsymmetrical diene (**X**>**Y**).

We recently published[5] a study on the ANDA adducts of sorbate ester (e.g., **2**) and sorbic alcohol derivatives—synthetically attractive because of the extra functionality built-in. We demonstrated, inter alia, a convenient synthesis of 5-methylornithine **3** as a single diastereoisomer from **2**. We now report the extension of our studies to other amino acid syntheses: we were particularly interested in the important hydroxyamino acid, (2*S*,5*R*)-δ-hydroxylysine **4** which is a significant constituent of collagen,[6] and frequently *O*-glycosylated as a mono or disaccharide.[7]



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doi:10.1016/j.tetlet.2010.02.076

Superficially it would appear that a sorbate derivative such as **5** with a built-in protected amino group is an ideal precursor of **4**, but there are two critical issues to address:

1. The conjugated ester group has a strong directing effect[4] in the ANDA and the undesired **P** adduct is overwhelmingly preferred.
2. A second electron-withdrawing group on the diene can easily shut down the ANDA reaction altogether: thus diesters of muconic acid such as **6** fail to react.[8]

Regarding point 1, it is possible to enforce the **D** adduct, wholly or in part, by using a tethered intramolecular ANDA in cases where the intermolecular reaction gives largely the **P** adduct, as shown by Russell and co-workers[9] and Sparks et al.[10] It was noteworthy in the latter case that extending the length of the tether again led to a regioisomeric mixture: further, introduction and removal of a tether inevitably generate extra steps. Point 2 is demonstrated by the complete unreactivity of phthalimide **5** (prepared in two steps from methyl sorbate[8]) under our standard ANDA conditions.[5] However, since sorbic *alcohol* derivatives react well under ANDA conditions, and the free alcohols give appreciable **D** regioisomer,[5,11] we aimed for a protected amino-alcohol related to **5** as a suitable substrate, and this allowed us to prepare **4** in a protected form as follows.

Successive Wittig reactions of Boc glycinal **7a** (Scheme 2) with stabilised phosphoranes afforded diene **9a** via enal **8a**, which was generally not isolated but reacted directly.[12] It is important to note that ester **9a**, like **5**, was *unreactive* in the ANDA reaction in our hands. DIBAL-H reduction of **9a** afforded the desired alcohol **10a** in a satisfactory yield together with a little (ca. 5%) of the partially reduced aldehyde. We also studied the corresponding series with benzyloxycarbonyl (Z) protection (**7b–10b**), though the yields were not as good, particularly in the DIBAL-H step; aldehyde **7b** was conveniently prepared by oxidation of Z-aminoethanol with trichloroisocyanuric acid and TEMPO.[13] Incidentally, we could not effect a satisfactory selective reduction of the ester functionality in phthalimide derivative **5**.

Alcohol **10a** reacted well in the ANDA reaction (Scheme 3) with either BocN=O or ZN=O generated in situ from the corresponding hydroxylamines: in common with other sorbic alcohol derivatives,[5] an organic oxidant ($Bu^n_4N^+\ IO_4^-$) in CH_2Cl_2 gave a better yield than $NaIO_4$ in aq MeOH. The **P** and **D** adducts **11a** and **12a** from BocN=O resulted in a total yield of 87% and a 45:42 ratio. Although it was in a sense disappointing that the desired distal isomer **12a** was marginally the minor product, the isomers were easily separated and a single crystal X-ray structural analysis confirmed the structure of **12a** (Fig. 1). We have described[5] the use of $^1H–^{15}N$ HSQC NMR as a useful tool for distinguishing **P:D** pairs: as noted therein, this technique has been applied to **11b/12b**, giving results consistent with the X-ray data for **12a**.

Similarly, reaction of **10a** with ZN=O gave a separable mixture of **11b** and **12b** (79%, **P**:**D** = 42:37). We were surprisingly unable to effect a direct oxidation of the primary alcohol in **12a** or **12b** under various conditions, although the proximal isomer **11b** was easily oxidised to the carboxylic acid using TEMPO-PhI(OAc)$_2$[14,15] in very satisfactory yield (61%). Instead, hydrogenation of **12b** effected deprotection of the Z group, saturation of the C=C bond and N–O cleavage. Without isolation, the intermediate amine was treated with Boc_2O and Na_2CO_3 to afford the bis-Boc protected diol **13** (30%). Finally, selective oxidation of **13** using TEMPO-PhI(OAc)$_2$ proceeded satisfactorily and bis-Boc δ-hydroxylysine (2*SR*,5*SR*) **14**

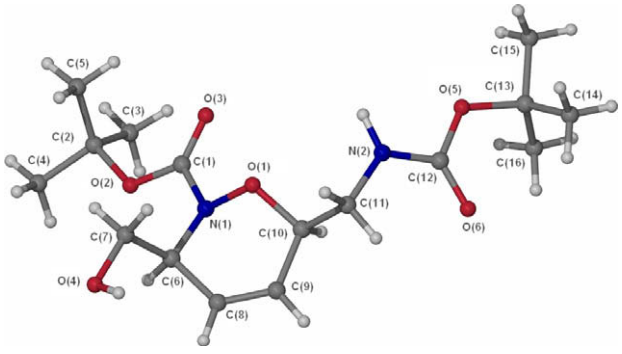
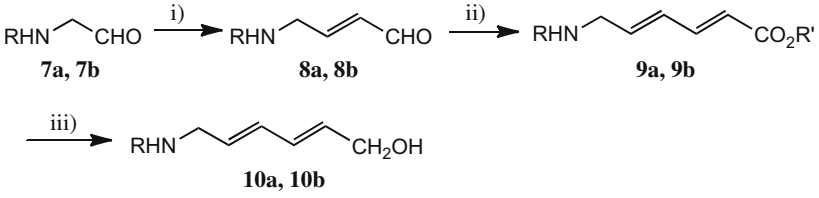
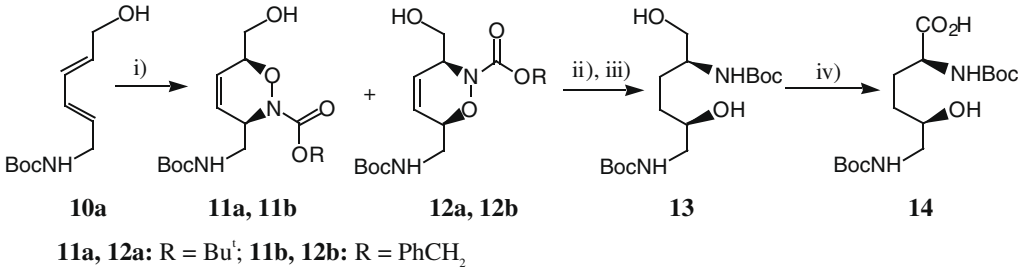


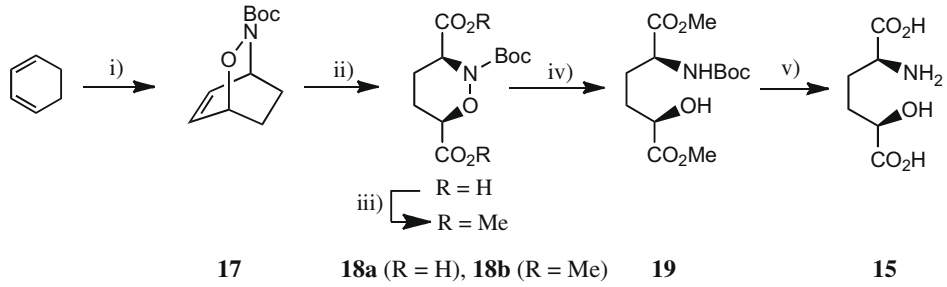
Figure 1. Single crystal X-ray structure of compound **12a** (CCDC 765959).



Scheme 2. Synthesis of diene intermediates for δ-hydroxylysine. Series a: R = Boc, R′ = Me; Series b: R = Z, R′ = Et. Reagents and conditions: [Series a] (i) Ph_3P=CHCHO, THF, reflux, 88%; (ii) Ph_3P=$CHCO_2Me$, THF, trace $PhCO_2H$, 20 °C, combined yield for steps (i) and (ii) 67%; (iii) Bu^i_2AlH, THF, −78 °C to −40 °C, 64%; [Series b]: (i), Ph_3P=CHCHO, THF, reflux, (ii) Ph_3P=$CHCO_2Et$, THF, trace $PhCO_2H$, 20 °C, combined yield for steps (i) and (ii) 58%; (iii) Bu^i_2AlH, THF, −78 °C to −40 °C, 38%.



Scheme 3. Completion of the δ-hydroxylysine synthesis. Reagents and conditions: (i) BocNHOH or ZNHOH, $Bu^n_4N^+\ IO_4^-$, CH_2Cl_2, combined isomers 87% [Boc], 79% [Z]; (ii) (on **12b**) H_2–Pd, THF; (iii) Boc_2O, aq THF, Na_2CO_3, 30% for steps (ii) and (iii); (iv) TEMPO, PhI(OAc)$_2$, aq MeCN, 22%.



Scheme 4. Synthesis of 2-amino-5-hydroxyadipic acid. Reagents and conditions: (i) BocNHOH, $NaIO_4$, 70%; (ii) $RuCl_3$, $NaIO_4$, PhMe/EtOAc/H_2O, 44%; (iii) $TMSCHN_2$, 100%; (iv) SmI_2, THF, 80%; (v) aq HCl, heat, 100%.

resulted in 22% yield. Commercial L-δ-hydroxylysine [viz. of (2*S*,5*R*) stereochemistry] was converted into bis-Boc derivative **14** for comparison and fully characterised: see Supplementary data.

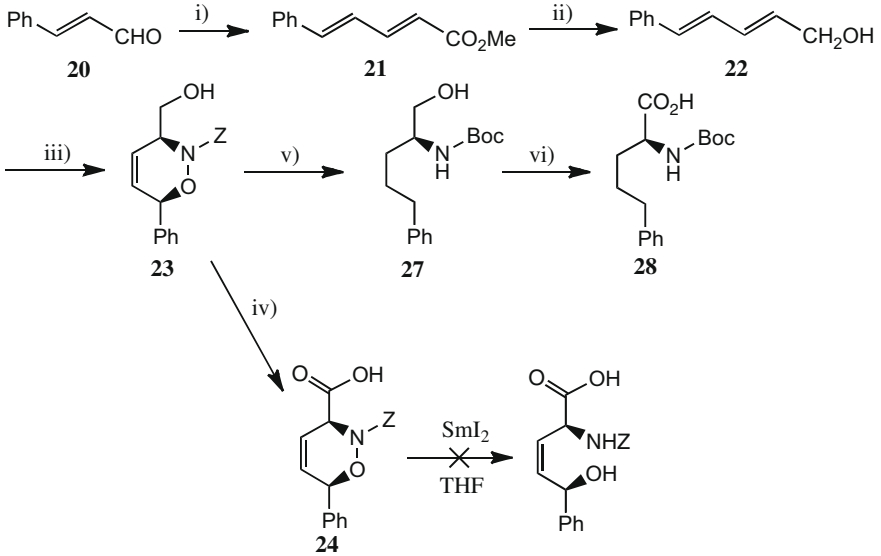
Previous syntheses of **4** have almost invariably proceeded via chiral pool intermediates, especially glutamic acid: for example, Allevi and Anastasia[16] reported a synthesis in 10 steps, involving diastereoisomer separation. The problem with this approach has been control of the relative stereochemistry between C(2) and C(5) of the α-amino acid.[17] Our synthesis clearly lacks a resolution, but since chiral versions of the ANDA are well known, using, for example, mandelic acid derivatives,[18] α-Cl nitroso sugars or camphor-derived nitroso derivatives, this aspect could be addressed: as noted above, the ANDA reaction ensures correct relative 2,5-stereochemistry.

We now describe the conversion of other types of ANDA adducts into α-amino acids, firstly 2-amino-5-hydroxyadipic acid **15**,[19] a known metabolite of **4** resulting from a PLP-mediated transamination and obtainable from a *symmetrical* ANDA adduct[21] (Scheme 4).

Thus cyclohexa-1,3-diene was reacted with BocN=O and the product **17** subjected to oxidative cleavage to afford the dicarboxylic acid **18a** reported by Procter and co-workers[21c] Cleavage of the N–O bond in compounds such as **18a** without the loss of the N-protecting group has been performed in many ways, for example, using $Mo(CO)_6/NaBH_4$, Raney nickel-H_2 or with SmI_2.[22–24] To improve solubility, the diacid was first converted into the dimethyl ester **18b** in a quantitative yield. SmI_2 reduction then proceeded very well in THF, the only significant issue being the removal of SmI_2 traces: the ring-opened product **19** was obtained in high yield. Finally, heating **19** in aq HCl at reflux afforded the desired diacid **15** as its HCl salt, essentially quantitatively.

Finally we describe an amino acid synthesis from an ω-phenyl ANDA adduct. This synthesis exploits an important feature of the reaction, namely the greater and reversed directing effect of a phenyl group, compared to alkyl, in unsymmetrical dienes (Scheme 1).[4,11] Thus, where X = CH_2OR, Y = Ph the **D** adduct is strongly favoured: Kouklovsky has reported similar examples.[11] We obtained the requisite diene (Scheme 5) by Wittig homologation of cinnamaldehyde **20** using $Ph_3P{=}CHCO_2Me$ ($Ph_3P{=}CHCHO$ did not react) followed by DIBAL-H reduction of known[25] ester **21**: the air-sensitive alcohol **22**[25] was obtained in an excellent yield but was best used at once. Under standard ANDA conditions (ZNHOH, $NaIO_4$, and aq THF) compound **23** was obtained in a satisfactory yield as the **D** adduct only; the mass balance was mainly unreacted **22**.

Interestingly, the use of organic-soluble periodate ($Bu^n_4N^+\ IO_4^-$) in CH_2Cl_2 gave no reaction here, being consistent with a lower intrinsic reactivity of all these ω-phenyl dienes compared to their sorbate counterparts. Thus neither ester **21** nor the *O*-acetate of **22** would react under our standard ANDA conditions.[26] Adduct **23** crystallised in a form suitable for a single crystal X-ray analysis, confirming its **D**-regiochemistry (Fig. 2). Here again, $^1H–^{15}N$ HSQC NMR gave the same conclusion.[5] Oxidation of **23** using TEMPO-$PhI(OAc)_2$ afforded the acid **24** in an excellent yield, but we could not selectively reduce the N–O bond with SmI_2 in this case (cf.



Scheme 5. Synthesis of homologated phenylalanine analogues via the ANDA reaction. Reagents and conditions: (i) $Ph_3P{=}CHCO_2Me$, PhMe, 20 °C, 80%; (ii) Bu^i_2AlH, CH_2Cl_2, 0 °C, 91%; (iii) ZNHOH, $NaIO_4$, aq THF, 0 °C, 50%; (iv) TEMPO, $PhI(OAc)_2$, aq MeCN, 80%; (v) Pd/C, H_2, THF, then Boc_2O, Na_2CO_3, 59%; (vi) TEMPO, $PhI(OAc)_2$, aq MeCN, 25%.

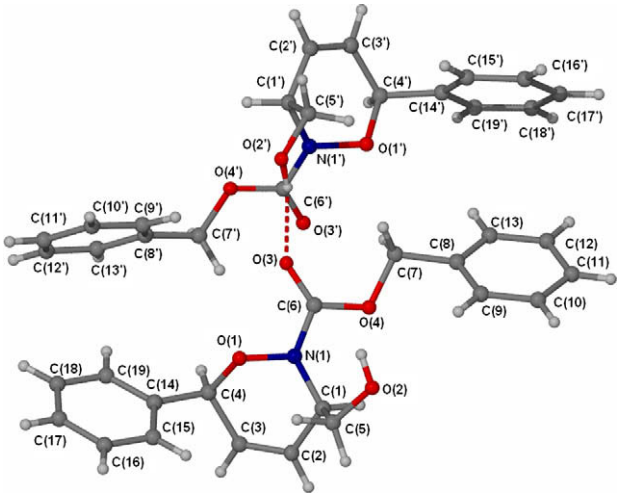
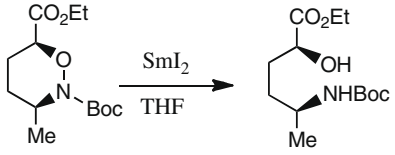


Figure 2. Single crystal X-ray structure of ANDA adduct **23** showing the noticeable intermolecular H bond (CCDC 725212).

Scheme 4, **18b**→**19**). We believe a more appropriate protecting group could solve this issue (and retain the extra functionality) as the sorbate-derived ANDA adduct **25** was smoothly reduced to **26**[8] (80%), and Keck et al. reported SmI_2 reductions where benzylic OH groups were retained.[24]



25 **26**

Instead (Scheme 5), exhaustive hydrogenation of **23**, including hydrogenolysis of the benzylic alcohol, followed by reprotection afforded amino-alcohol **27** in a satisfactory yield. Finally, TEMPO-PhI(OAc)$_2$ oxidation afforded the known Boc amino acid **28**;[27,28] the Me ester of **28** was previously made via Heck chemistry.[20]

In summary, we have demonstrated syntheses of three structurally diverse α-amino acids **14**, **15** and **28** as single diastereoisomers using the ANDA reaction. Careful attention to the reactivity and regiochemical preference of each diene, particularly when unsymmetrical, is essential. In particular a novel, concise synthesis of the important collagen constituent δ-hydroxylysine in a protected form is shown.

Acknowledgements

We are grateful to the EPSRC for a DTA award to L.B. and the University of Liverpool for consumables grants to D.O'F. and S.W. (M. Chem. projects, 2007–8 and 2008–9). We also thank Professor Richard Taylor (University of York) for valuable discussions on diene synthesis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.076.

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28. In retrospect, we believe that the rather low yields obtained in the oxidations of **13** to **14** and **27** to **28** may have been due to the batch of TEMPO employed. As given above, a similar oxidation of **23** to **24**, using a new batch of TEMPO and performed later, gave a very good yield of 80%, and this is probably the expected yield for the other TEMPO oxidations.