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Synthesis of densely functionalized pyrrolidinone templates by an intramolecular oxo-Diels–Alder reaction

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Abstract—Preparation of densely functionalized pyrrolidinone templates, is a challenge for synthetic chemists. These templates are important building blocks for novel conformationally constrained natural products or for library generation of highly functionalized bi or polycyclic compounds. We discovered that trienes **6a–j** undergo facile stereoselective intramolecular Diels–Alder reactions to generate densely functionalized *cis* fused pyrrolidinone templates **1a–j**. These reactions allow for directed remote hydroxylation with complete control of stereochemistry.

1. Introduction

Densely functionalized pyrrolidinone templates are a challenge for the synthetic chemist. These templates are important building blocks for library generation of peptidomimetic compounds.[1] An efficient way to address this challenge is the intra-molecular Diels–Alder (IMDA) reaction using appropriately designed trienes.[2] The IMDA reaction is often superior to the intermolecular Diels–Alder reaction with regard to reactivity and selectivity.[1] The tether connecting the diene and dienophile reactive partners could vary substantially.[2a–d] Herein we report the short, efficient entry into a class of complex pyrrolidinone templates (Scheme 1).

Recently we have utilized electrocyclic reactions of amino acid derived trienes to produce densely functionalized octahydroquinolines and hexahydroisoindoles.[2a,b] The chemistry is also adaptable to solid support and has been used to generate libraries of considerable complexity. These Diels–Alder reactions are carried out in solution or on solid support and allow for the control of facial selectivity, *endo* versus *exo* selectivity and stereochemical selectivity at most of the ring positions. Based on this work we began to examine oxo-Diels–Alder reactions to generate remotely hydroxylated pyrrolidinone analogs.[3]

2. Results and discussion

Trienes **6a–j** were prepared in five steps from NH-Boc protected L-amino acids using a modification of our amino acid derived triene preparation protocol.[4] The corresponding Weinreb amides **2a–e** from the acids were prepared in 87–92% yield via a mixed anhydride using NMM, isobutyl chloroformate and *N*-methyl-*N*-methoxy hydroxyl amine hydrochloride. The amides **2a–e** then were reduced to the desired aldehydes **3a–e** by LAH at −78°C.[5] The desired aldehydes were the only isolated products in 80–85% yields. These aldehydes did not undergo racemization when stored briefly at 4°C. On treatment of **3a–e** with triethyl phosphonoacetate in presence of potassium *t*-butoxide in THF the unsaturated ester **4a–e** were produced in 70–75% yields without any detected racemization.[6] The corresponding amine derivatives were prepared by treatment with 50% TFA, which were then benzylated using $CsCO_3$/BnBr in dry methylene chloride to afford the products **5a–e** in 76–82% yields. The triene precursors **6a–j** were prepared by coupling of the requisite keto acid to the *N*-benzyl protected unsaturated esters. Compounds **5a–e** in 80–84% yields. The intramolecular Diels–Alder reactions of **6a–j** were carried out at reflux in dry toluene. Unprotected (NH) containing trienes **6** did not produce any cycloaddition products after reflux in toluene for 72 h and slowly decomposed when refluxed over a longer period of time. Although there are four possible isomers only the *cis* fused isomers **1a–j** were isolated. It appears that the intramolecular Diels–Alder reaction of these trienes proceeds with *exo*-selectivity to give the *cis*-fused pyrrolidinone templates.

Keywords: intramolecular hetero Diels–Alder reaction; remote hydroxylation; pyrrolidinone.

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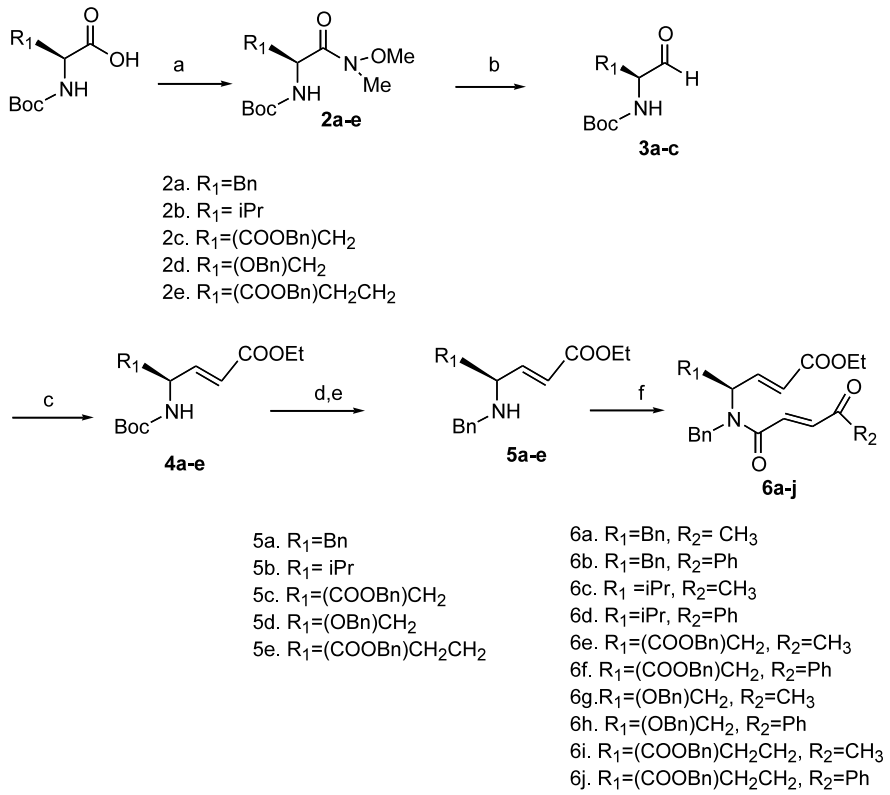


Scheme 1. *Reagents and conditions*: (a) IBCF, NMM, Me–N(OMe)H·HCl, CH_2Cl_2; (b) LAH, THF, −78°C; (c) K*t*BuO$^-$, triethyl phosphonoacetate, THF; (d) 50% TFA, rt; (e) $CsCO_3$, BnBr, CH_2Cl_2; (f) 3-acetyl acrylic acid or 3-benzyl acrylic acid, HOAT, EDCI, 0°C.

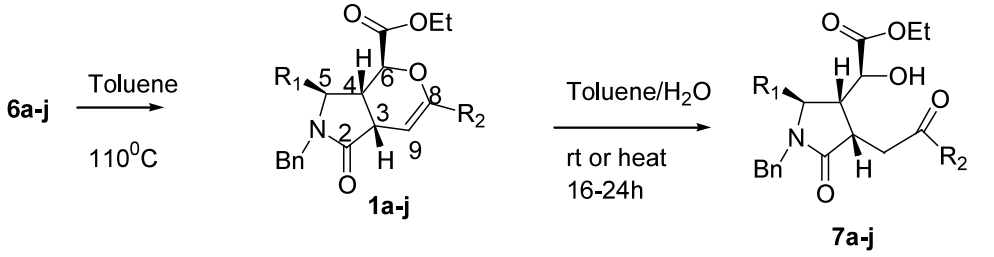
Compounds **1a**–**j** slowly undergo hydrolysis at room temperature in wet toluene to produce the hydroxy-acetic acid, ethyl ester derivative of pyrrolidinones **7a**–**j**. Stereochemical assignments at the pyrrolidinone rings **1a**–**f** at the alkyl and ester branched centers were made based on two-dimensional NMR experiments.

Initially, COSY experiments were used to locate the position of the different protons. The protons at the 5- and 6-positions overlapped with each other in deuterated chloroform, but they were resolved in acetonitrile.[7] A series of NOESY experiments followed by HMBC and HMQC were then carried out. These experiments helped determine the relative stereochemistry of each ring positions.

We observed a strong transfer of magnetization between protons at the 4- and 3-positions (Fig. 1, structure 1). The proton at the 4- and 3-positions also had strong transfer of magnetization with the benzylic protons of the amino acid moiety. No transfer of magnetization was observed between the proton at the 5-position and the proton at the 3-position. No NOE was also observed between the protons at the 4-position and the benzylic protons of the benzyl group attached to the nitrogen. In each case the coupling constant between the protons at C-3 and C-4 is 8.0 Hz which is consistent with *cis* ring juncture. The coupling constant between the protons at C-4 and C-6 is 8.6 Hz and is consistent with the ester group in the orientation shown. The coupling constant between the proton on C-4 and C-5 is 2.5 Hz, which is consistent with the orientation shown. Based on this data we believe that the ring junction is *cis* with the protons at C-3 and C-4 coming out of the plane of the page. We also believe that both the amino acid R group and the ester are on the same face of the molecule as the ring protons. Since a single diastereomer is produced by this approach we have been unable to compare the products produced with the other possible isomers.[8] Work is continuing to establish conditions for other isomeric products.

We believe our synthetic protocol will give versatile access to a wide range of pyrrolidinone analogs, allowing the synthesis of a novel class of conformationally restricted polycyclic compounds both on and off the solid support.

Preparation of 1a: The triene (0.181 g, 0.44 mmol) was dissolved in dry toluene (8 mL). The reaction mixture was refluxed for 16 h. The residual toluene was then removed in vacuo. After chromatography **1a** (0.164g, 0.40 mmol, 91%) was isolated by eluting the desired compound with 10–20% EtOAc/CH_2Cl_2. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.20 (t, J=7.14, 3H), 1.85 (s, 3H), 2.48 (ddd, J=3.41, 8.6 Hz, 1H), 2.65 (m, J= 13.82, 3.41, 1H), 2.85 (m, 1H), 3.05 (dd, J=13.82, 4.27, 1H), 3.52 (m, 2H), 3.95 (q, J=7.16, 2H), 4.01 (d, J=14.82, 1H), 4.85 (d, J=4.27, 1H), 5.15 (d, J=14.82, 1H), 7.01–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz), d: 14.3, 20.1, 37.5, 37.8, 38.7, 44.9, 58.2, 61.8, 73.8, 94.4, 127.5, 128.2, 128.6, 129.2, 129.3, 129.6, 136.3,



1a,7a. R_1= CH_2Ph, R_2 = CH_3
1b,7b. R_1= CH_2Ph, R_2 = Ph
1c,7c. R_1= iPr, R_2 = CH_3
1d,7d. R_1= iPr, R_2 = Ph
1e,7e. R_1= $(COOBn)CH_2$, R_2 =CH_3

1f,7f. R_1= $(COOBn)CH_2$, R_2 =Ph
1g,7g. R_1=$(OBn)CH_2$
1h,7h. R_1=$(OBn)CH_2$
1i,7i. R_1=$(COOBn)CH_2CH_2$
1j,7j. R_1=$(COOBn)CH_2CH_2$

Compounds	yields 1 a-f	yields 7a-f
1a, 7a	91 %	78%
1b, 7b	85%	77%
1c, 7c	87%	80%
1d, 7d	76%	83%
1e, 7e	72%	72%
1f, 7f	78%	75%
1g, 7g	63%	68%
1h, 7h	67%	69%
1i, 7i	74%	71%
1j, 7j	73%	75%

Figure 1. IMDA products from the triene precursors.

136.6, 152.3, 169.6, 174.1 The LC/MS calculated: 405.2 found $(M+H)^+=406.2$, found $(M+Na)^+=428.2$, HRFABMS $(M+H)^+$ calculated = 405.2011, found 405.2018; $[\alpha]_D^{20}$ +58 (*c* 0.10, $CHCl_3$).

Preparation of 7a: The cycloaddition product **1a** (0.11g, 27 mmol) was dissolved in toluene (5 mL) and water (0.5 mL). The reaction mixture was stirred for 16 h. The residual toluene/H_2O was then removed in vacuo. After chromatography **7a** (0.089 g, 0.21 mmol, 78%) was isolated by eluting the desired compound with 20% EtOAc/CH_2Cl_2. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.21 (t, $J=7.12$, 3H), 1.75–1.85 (m, $J=13.70$, $J=3.31$, 1H), 1.98 (s, 3H), 2.30 (m, 1H), 2.55 (dd, $J=13.75$, $J=3.41$, 1H), 2.70–2.98 (m, 2H), 3.31 (bs, OH), 3.60 (m, 2H), 3.90 (m, 1H), 4.10 (m, 2H), 4.15 (d, $J=14.90$, 1H), 5.00–5.10 (d, $J=14.90$, 1H). 6.85–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 22.7, 29.3, 30.0, 37.5, 38.6, 43.8, 44.8, 59.1, 62.1, 71.1, 126.7, 127.0, 127.5, 127.7, 128.0, 128.5, 128.7, 129.1, 129.9, 135.9, 136.3, 138.6, 173.1, 175.0, 207.3. LC/MS calculated: 423.2, found 423.2, and $(M+Na)^+=446.2$. $[\alpha]_D^{20}$ +78 (*c* 0.32, $CHCl_3$).

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6. Compounds **4a–c** were compared to identical compounds from racemic aldehyde and no racemization was detected by chiral HPLC.
7. While protons on C-5 and C-6 were resolved they were too close to accurately observe NOEs between them.
8. By chiral HPLC.