Potential of (2*E*,7*E*)-Nonadienedioates in Asymmetric Synthesis: Construction of Homopipecolic Acid and an Aminoester Building Block for Peptide Nucleic Acids

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Dedicated with respect and affection to Gerry Pattenden, an inspiring scientist, on the occasion of his 70th birthday

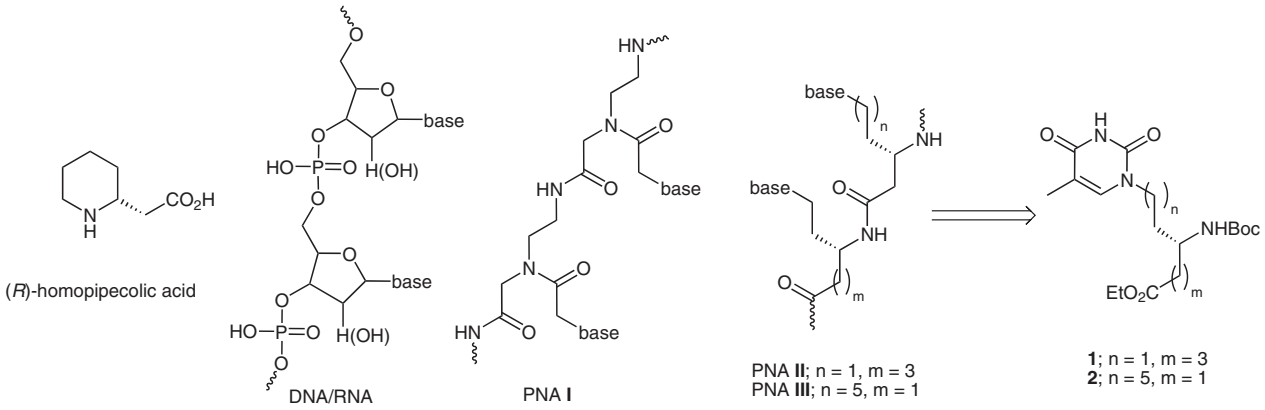
Abstract: A convenient, asymmetric synthesis of (*R*)-homopipecolic acid methyl ester and an homochiral peptide nucleic acid (PNA) monomer building block are described, starting from the orthogonally disubstituted (2*E*,7*E*)-nonadienedioate. The approach involves stereoselective Michael monoaddition of (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to the unsaturated ester as the key step, and subsequent transformation of the remaining double bond of the unsaturated acid.

Key words: β-amino acids, asymmetric synthesis, Michael additions, PNA, homopipecolic acid, orthogonally substituted dienedioate

Every synthetic route starts from a particular substrate that lends itself to the retrosynthetic scheme planned. The capacity of a substrate to participate in a wide range of synthetic pathways depends on the potential of their structure: cycles, chains and functional groups. Molecules with functional groups that react selectively are attractive from this point of view: the better the chemical orthogonality of the functional groups, the larger the spectrum of synthetic transformations possible and, consequently, the range of accessible targets.

Cyclic β-amino acids such as (*R*)-homopipecolic acid (Scheme 1) have a number of interesting features that have been used to develop synthons of natural products[1] and key intermediates in β-lactam structures.[2] Synthetic oligonucleotides (Scheme 1; DNA/RNA) have been considered as potential gene-targeted therapeutic agents (antisense and antigene).[3] Peptide nucleic acids (PNAs) were first reported in 1991 as DNA mimics[3c] and, since this time, a vast number of studies have been reported covering their synthesis, properties and potential applications. Among the known oligonucleotide analogues, acyclic *N*-(2-aminoethyl)glycyl peptide nucleic acids (Scheme 1; PNA **I**) or those derived from base-containing δ-amino acid derivatives[4] (Scheme 1; PNA **II**), are found to be very good mimics of DNA/RNA. Within this area, a steadily growing group of analogues in which the sugar–phosphate backbone is replaced by a polyamide backbone, is emerging, mainly as a consequence of the intriguing base-pairing properties of their prototype PNA. In this context, we envisaged the synthesis of the amino acid building block mononer **2** in PNA **III**.

We have demonstrated[5] the use of chiral lithium (α-methylbenzyl)benzylamide [(*R*)-**3** or (*S*)-**3**] to initiate asymmetric conjugate addition cyclisation of octa-2,6-dienedioate and nona-2,7-dienedioate to generate chiral cyclopentane and cyclohexane derivatives **4** and **5**, respectively.[5b–e] We have also developed strategies to stereoselectively obtain double- (**7**) and mono-addition (**6**, **8**, **9** and **10**) products[5d] (Scheme 2), where the *Z*-double bond



Scheme 1

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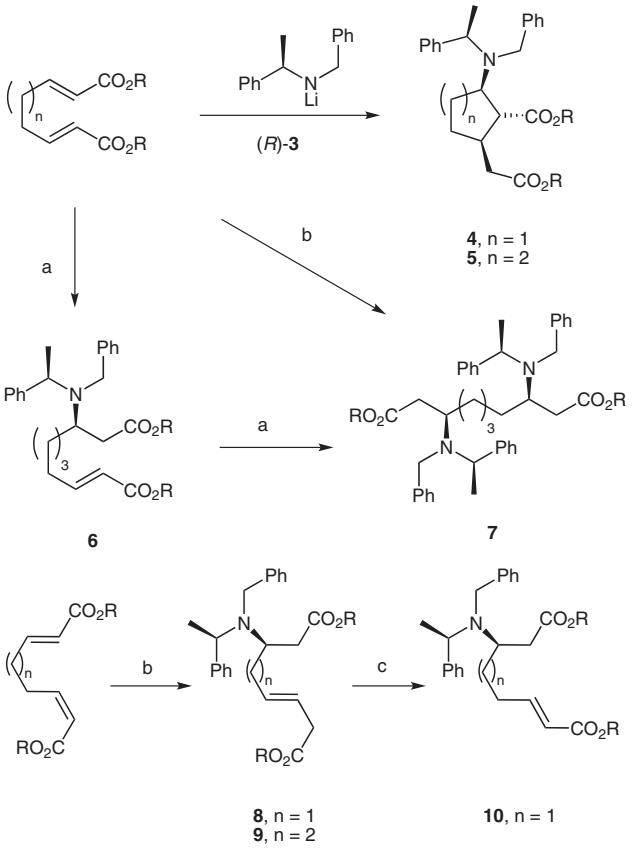
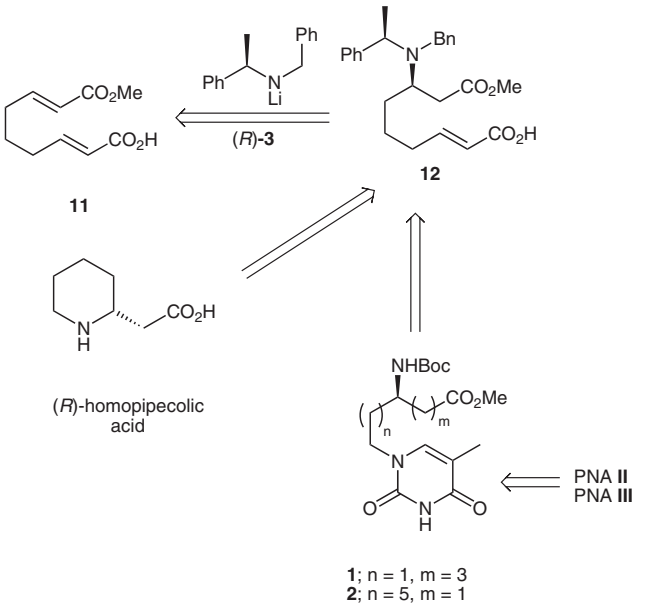
plays a crucial role on the (*Z*,*E*)-dienedioate as a vehicle for γ-deprotonation. We have proposed **9** to be an intermediate in an approach to **1**.[5a]

Here, as shown in the retrosynthetic analysis (Scheme 3), we focused on the potential of (2*E*,7*E*)-nonadienedioate **11** as an orthogonally functionalised starting material in which the groups show differing reactivity towards lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide [(*R*)-**3**]. This selectivity is exploited synthetically by modifying the residual functionality to give either homopipecolic acid methyl ester (formerly synthesised using other protocols[6]) or to construct a thymine long-chain β-amino acid PNA monomer **2** for use in oligomerisation to form PNA. Both goals were developed in an enantiocontrolled way.



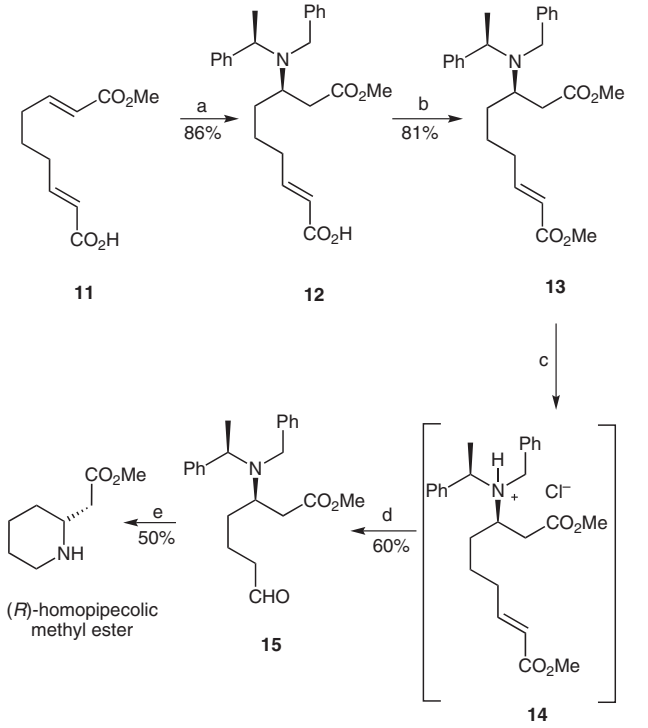
Scheme 2 Reagents and conditions: (a) (*R*)-**3** (1.2 equiv), THF, –78 °C; (b) (*R*)-**3** (3 equiv), THF, –78 °C; (c) *t*-BuOK, *t*-BuOH.

The synthesis of homopipecolic methyl ester (Scheme 4) started with addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide [(*R*)-**3**] to the orthogonally functionalised substrate **11**, to provide adduct **12** (de >95%)[7] stereoselectively (*vide infra*) in good yield, in accordance with the literature.[8] Acid salt generation enriches electron-density on the conjugated olefin, averting nucleophilic attack at this centre. The next step required ozonolysis of **12**, however, since reports in the literature recommended prior esterification,[9] **12** was treated with $TMSCHN_2$ to provide the corresponding diester **13**.[10] Attempts at ozonolysis of **13** were unsuccessful, leading instead to decomposition of the starting material as a consequence of *N*-oxide

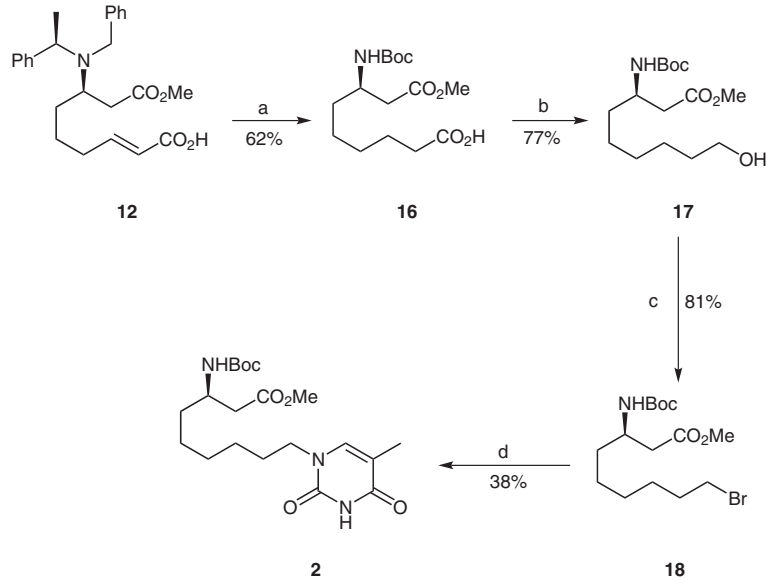


Scheme 3 Proposed strategy for the synthesis of (*R*)-homopipecolic acid and monomers **1** and **2** for PNA synthesis

formation[11] provoking a Cope elimination. However, treatment of **13** with anhydrous HCl followed by ozonolysis and reduction with Me_2S gave aldehyde **15**. Finally, hydrogenolytic debenzylation over Pearlmans catalyst induced cyclisation to the imine, which underwent reduction to (*R*)-homopipecolic methyl ester in situ {$[\alpha]_D^{26}$ –3.6 (*c* 0.32, $CHCl_3$); Lit.[6c] for the enantiomer $[\alpha]_D^{26}$ +3.9 (*c* 0.64, $CHCl_3$)} in 50% overall yield.



Scheme 4 *Reagents and conditions*: (a) Lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamine [(*R*)-**3**; 3.6 equiv], THF, –78 °C; (b) $TMSCHN_2$, benzene–MeOH (1:1), 30 min; (c) HCl (g); (d) O_3, then Me_2S; (e) $Pd(OH)_2/C$, H_2 (4 atm), EtOAc.



Scheme 5 *Reagents and conditions*: (a) $Pd(OH)_2/C$, H_2 (4 atm), Boc_2O, EtOAc, 3 d; (b) BH_3·THF, THF, 20 °C, 60 min; (c) CBr_4, Ph_3P, CH_2Cl_2, 45 min; (d) thymine, TBAI, K_2CO_3, DMF, 70 °C, 6 h.

The route towards the PNA monomer started from **12** (Scheme 5). Reacting a mixture of **12**, Boc_2O and Pearlmans catalyst in ethyl acetate for three days under hydrogen (4 atm), accomplished a one-pot amine-debenzylation, Boc-reprotection and hydrogenation of the olefin in 62% yield. Subsequent selective reduction of the carboxylic acid with borane, followed by treatment with CBr_4/PPh_3, and finally, treatment with thymine, K_2CO_3, and TBAI in refluxing DMF[12] provided the target compound **2**.[13] However, the poor nucleophilicity of thymine resulted in a relatively low yield in the final displacement (38%).

In summary, we have achieved the synthesis of two valuable products as important building blocks: (*R*)-homopipecolic methyl ester and a PNA-monomer containing a long-chain β-amino acid backbone. Both products were elaborated in a divergent fashion starting from (2*E*,7*E*)-nonadienedioate monoester **11**, which is a readily accessible bifunctional substrate that exhibits orthogonal behaviour towards aza-Michael stereocontrolled addition of chiral lithium (α-methylbenzyl)benzylamide. The residual functionality can then undergo a range of possible synthetic transformations, demonstrating the power of this protocol.

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(7) Analysis of the crude product by ^1H NMR (400 MHz) confirmed it to be diastereomerically pure as no trace was found of any other stereoisomer. An ee >95% is consistent with the high optical purity of the lithium amide used.

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(10) Analysis of the crude product by ^{1}H NMR (400 MHz) confirmed it to be diastereomerically pure as no trace was found of any other stereoisomer. The (2*S*,α*R*) diastereisomer has been prepared by non-stereoselective monoaddition of α-methylbenzylamine to (2*E*,8*E*)-decadienedioate followed by treatment with benzyl chloride. See ref. 5d
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(13) **Typical procedure:** A suspension of thymine (108.6 mg, 0.861 mmol), TBAI (34.4 mg, 0.086 mmol) and K_2CO_3 (59.6 mg; 0.431 mmol) in DMF (5 mL) was stirred for 30 min, then heated to 70 °C for 30 min. Bromide **18** (17 mg, 0.04 mmol) was added and the resulting mixture was stirred for 6 h at 70 °C. Then the mixture was cooled to 0 °C, filtered through Celite® and the filter pad was washed with EtOAc. The filtrate was washed with H_2O, dried over anhydrous Na_2SO_4, filtered and the solvent was removed. Purification of the crude product by flash chromatography (hexane–Et_2O, 1:4) provided **2** (8 mg, 38%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.57 (m, 10 H, H-4, H-5, H-6, H-7, H-8), 1.42 [s, 9-H, $C(CH_3)_3$], 1.92 (s, 3 H, Me-C5′), 2.50 (m, 2 H, H-2), 3.65–3.70 (m, 2 H, H-9), 3.67 (s, 3 H, OCH_3), 3.89 (m, 1 H, H-3), 4.93 (d, *J* = 8.7 Hz, 1 H, NH), 6.97 (s, 1 H, H6′), 8.22 (s, 1 H, H-3′). IR (neat): 3365, 2931, 2857, 1736, 1712, 1483, 1366, 1166, 1094 cm^{-1}. ^{13}C NMR (200 MHz, $CDCl_3$): δ = 12.59, 26.12, 26.48, 28.60, 29.10, 32.14, 34.71, 39.44, 47.62, 48.70, 51.87, 77–79, 110.78, 140.67, 150.93, 164.33, 172.38. HRMS: *m*/*z* calcd for $C_{20}H_{33}N_3O_6$: 434.2261; found: 434.2260.