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Enantioselective syntheses of orthogonally protected tricarballylic acid esters

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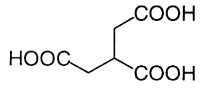
Abstract

3(*S*) and 3(*R*)-Benzyloxycarbonyl-pentanedioic acid mono-*tert*-butyl esters (**6**) were obtained as enantiopure orthogonally protected tricarballylic acid (TCA) esters. These were synthesised by alkylation of the sodium enolate derived from chiral but-3-enoyloxazolidinone imides (**3**) with *tert*-butyl bromoacetate; following the hydrolysis to remove the chiral auxiliary, benzyl esterification afforded the 2-allyl succinic acid diesters (**4**) that were converted to protected TCA esters after oxidation of the double bond.

Keywords: alkylation; asymmetric synthesis; carboxylic acids; oxazolidinones; protecting groups.

Tricarballylic acid (TCA) (**1**) has a framework that bears structural similarity to several biologically active compounds such as citric acid, amino acids,[1a] toxins[1b] and enzyme inhibitors.[1c] In particular, TCA has attracted the attention of several research groups[2a,b] because it was found as a fragment in the mycotoxins, Fumonisins B_1 and B_2, isolated from the corn pathogen *Fusarium moliniforme*, which have been linked to human esophageal cancer in part of China and Southern Africa. To investigate the role that the TCA framework should play in other biologically active compounds, we decided to use it as a building block in our medicinal chemistry projects.[3] However, major synthetic problems arose from the necessity to use orthogonal protection on the carboxylic groups of TCA.



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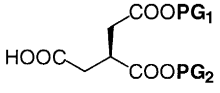

2

PG = protecting group

Previous syntheses of both enantiomers of dimethyl tricarballylic acid were described by Boyle and Kishi[2a] using a modified Hanessian procedure for the asymmetric Michael addition of a chiral allylphosphonoamide to *t*-butyl sorbate as a key step.[4] However, the resulting TCA dimethyl ester was not suitable for our purposes due to lack of orthogonality between the two ester groups. Subsequently

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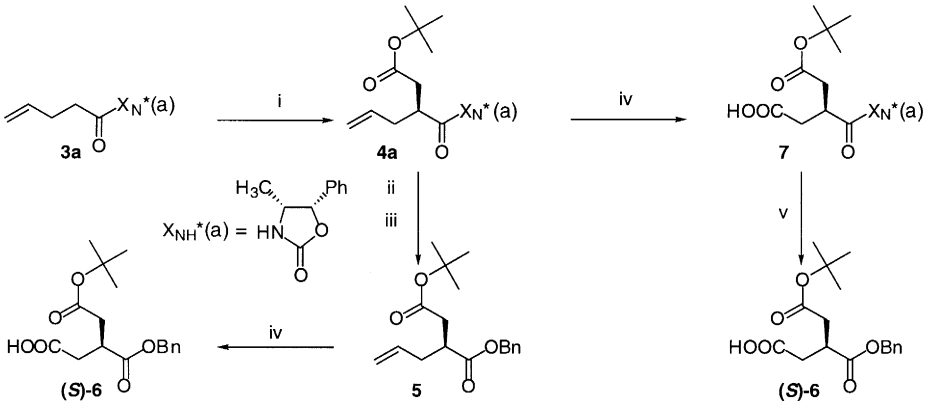
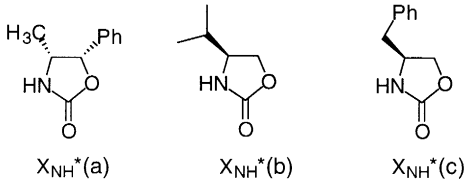
Wyatt et al.[5] demonstrated that but-3-enoyloxazolidinones (of type **3**, Scheme 1) bearing an Evans chiral auxiliary are able to undergo diastereoselective alkylation by various electrophiles of type Br–CH_2–X (X=CN, COOMe), and the homologue of aspartic acid was synthesized stereoselectively. With this in mind, the enantioselective synthesis of orthogonally protected TCA was planned as depicted in Scheme 1; *t*-butyl and benzyl esters were selected as protecting groups,[6] leaving the third carboxylic functional group unprotected (to obtain type **2** molecules). The allylic double bond of but-3-enoyloxazolidinones **3a** was used as a masked carboxymethyl group and diastereoselective alkylation was performed using *t*-butyl bromoacetate as the electrophile (recently Evans et al. reported a study on this kind of reaction).[7] The resulting compound **4a** was transformed into the target compound **(*S*)-6** by route ii–iii−iv or iv–v. In the first route the chiral auxiliary was removed from **4a** using $LiOH/H_2O_2$/THF and, after work-up, the resulting crude intermediate was esterified by *O*-alkylation with benzyl bromide/Cs_2CO_3. The oxidation of compound **5** with $RuCl_3/NaIO_4$ in a biphasic system[8] afforded the target compound **(*S*)-6** in 29% overall yield after flash chromatography.[9]



Scheme 1. (i) $BrCH_2CO_2{}^tBu$, NaHMDS, THF, −78°C (89%); (ii) $LiOH/H_2O_2$, THF, 0°C; (iii) Cs_2CO_3, BnBr, DMF (66%); (iv) $NaIO_4/RuCl_3 \cdot H_2O$, CCl_4/MeCN/H_2O (49%); (v) BnOLi/BnOH, THF

In the alternative route the oxidation of the double bond of compound **4a** with the chiral auxiliary in place gave a poor yield due to the difficulty of extraction of intermediate **7** from inorganic salts. The subsequent removal of the chiral auxiliary was effected by in situ benzyl esterification[10] using freshly prepared $PhCH_2OLi$ in benzyl alcohol/THF. Although this route also furnished the expected compound **6** the separation from side-products and excess $PhCH_2OH$ was, however, very tedious and the yield also low. Using oxazolidinones a, b, c and steps ii–iii–iv both enantiomers **(*R*)-6** and **(*S*)-6** were obtained (Table 1).



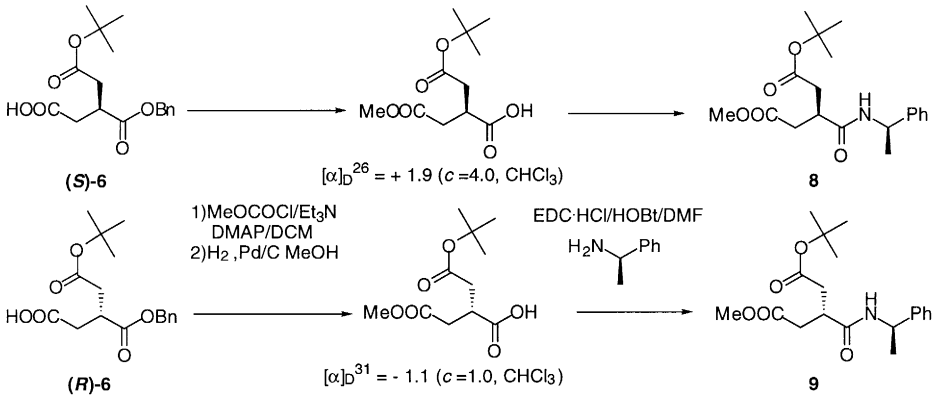
In order to establish the enantiomeric excess of the TCA derivatives the Chiral Derivatising Agents (CDAs) method was used and the resulting diastereoisomer ratio was checked by ^1H NMR. The derivatisation of both **(*R*)-6** and **(*S*)-6** with D(+)-norephedrine, D(+)-methylbenzylamine and (−)-menthol did not give unequivocal results due to large overlapping of proton signals and poor magnitude of the chemical shift differences. To improve the signal shift and to simplify the ^1H NMR spectra the free carboxylate functional group was converted into the corresponding methyl ester and, after deprotection of

Table 1

Entry	Product	Yield%[a]
3a	(*S*)-6	29
3b	(*R*)-6	12
3c	(*R*)-6	25

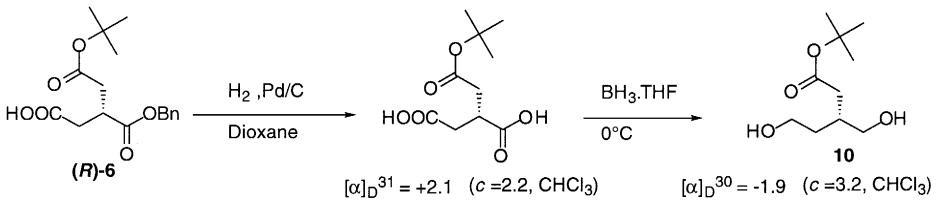
a: overall yield from acyloxazolidinone

the benzyl ester, CDAs were used on the free carboxyl group nearest to the stereocentre. The procedure is described in Scheme 2. The methyl ester signals of compounds **8** and **9** show ^{1}H NMR resonances at 3.59 and 3.69 ppm, respectively, and they were used to determine the ee of **(*S*)-6** and **(*R*)-6**.[11] Mutual addition of the NMR sample **8** to **9**, and vice versa, confirmed the assignment of the methyl ester resonance signals. The diastereomeric ratio Ds **8**:**9** was 92:8 for **8** and 3:97 for **9**.



Scheme 2.

The absolute stereochemistry of compound **(*R*)-6** was correlated with a compound of known absolute stereochemistry. Compound **(*R*)-6** was transformed (Scheme 3) in two steps into diol **10**: $[\alpha]_D^{30}$ −1.9 (*c*=3.2, $CHCl_3$), $[\alpha]_D$ −2.7 (*c*=2.5, $CHCl_3$) lit.[2a] and $[\alpha]_D$ +2.2 (*c*=2.6, $CHCl_3$) lit.[2a] for the enantiomer. The values of the optical rotation are very low and they were intended only from a qualitative point of view to confirm the sign of optical rotation and so to correlate the absolute configuration of the TCA derivatives with the reference compound.



Scheme 3.

In conclusion, an easy and approachable synthesis of both enantiomers, with good optical purity, of tricarballylic acid (TCA) has been described. This synthesis also provides final products with orthogonal protection in at least two out of the three carboxylic acid groups which renders the TCA moiety amenable to regioselective insertion into larger molecules. Applications of these enantiomerically enriched TCA derivatives as chiral building blocks for the synthesis of target compounds of medicinal interest is currently under investigation

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9. Compound (*S*)-**6**, pale yellow oil, ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, 9H), 2.46–2.90 (m, 4H), 3.18–3.35 (m, 1H), 5.14 (s, 2H), 7.28–7.45 (m, 5H), 8.8 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.0, 35.2, 36.5, 37.6, 66.9, 81.2, 128.1, 128.2, 128.5, 135.7, 170.4, 173.1, 176.5. Anal. calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.23; H, 6.89.
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11. Compound **8**, colourless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.44 (d, J=7.8 Hz, 3H), 2.33–2.45 (m, 2H), 2.61–2.74 (m, 2H), 3.08 (m, 1H), 3.59 (s, 3H), 5.02–5.11 (m, 1H), 6.37 (d, J=7.5 Hz, 1H), 7.20–7.29 (m, 5H); MS ES$^+$ m/z 349.8 (MH^+). Anal. calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.43; H, 7.84; N, 4.07. Compound **9**, colourless oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 1.45 (d, J=6.8 Hz, 3H), 2.30–2.74 (m, 2H), 2.52–2.62 (m, 1H), 2.71–2.82 (m, 1H), 3.02–3.12 (m, 1H), 3.69 (s, 3H), 5.02–5.10 (m, 1H), 6.45 (d, J=8.2 Hz, 1H), 7.18–7.30 (m, 5H); MS ES$^+$ m/z 349.8 (MH^+). Anal. calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.25; H, 7.81; N, 3.97.