A new enantiodivergent procedure utilising the chemoselective Dieckmann-type cyclisation of chiral mono-thiol diesters

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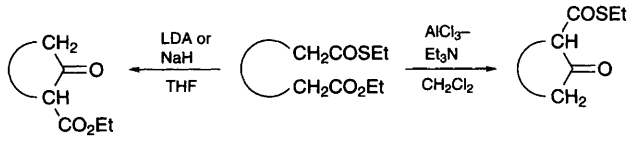
The chiral mono-thiol diester, 1 or 2, is converted to the corresponding enantiomeric cyclised products, (−)-7 and (+)-7 or (−)-9 and (+)-9, depending on whether LDA or $AlCl_3$–Et_3N is used.

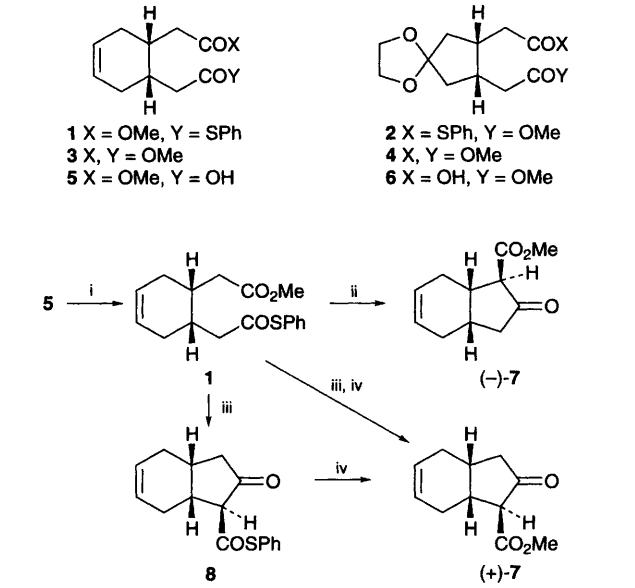
Recently we demonstrated that the Dieckmann-type cyclisation reactions of various dicarboxylic acid derivatives were readily promoted by using Lewis acids such as $AlCl_3$, $MgBr_2$, $MgCl_2$ and $Sn(OSO_2CF_3)_2$ in the presence of Et_3N or *N*-ethylpiperidine.[1] Among these Dieckmann-type reactions, the cyclisation mode of mono-thiol diesters employing $AlCl_3$–Et_3N proved to be different from that of the same compounds employing LDA or sodium hydride as shown in Scheme 1.[1] Thus, we anticipated new enantiodivergent procedures based on the chemoselective cyclisation mode of chiral mono-thiol diesters **1** and **2** under different Dieckmann-type reaction conditions as shown in Schemes 2 and 3.

Known chiral monoesters **5**[2] (98% ee†) and **6**[2] (94% ee†), obtained by enzymatic hydrolyses of diesters **3** and **4** with porcine pancreatic lipase or porcine liver esterase,[2] were treated with thiophenol (1.1 equiv.) in the presence of *N*,*N*′-carbonyldiimidazole (CDI) (1.1 equiv.) in THF to give the corresponding mono-thiol diesters **1** {77% yield, colourless oil, $[\alpha]_D^{21}$ −4.5 (*c* 0.69, $CHCl_3$)}[3] and **2** {90% yield, colourless needles (CH_2Cl_2–hexane), mp 64.5–65.5 °C, $[\alpha]_D^{23}$ +31.9 (*c* 0.99, $CHCl_3$)}, respectively. Treatment of **1** with LDA (2.5 equiv.) in the presence of HMPA (1 equiv.) in THF at −55 °C gave the known cyclised product (−)-**7** {68% yield, 96% ee,‡ $[\alpha]_D^{27}$ −154.7 (*c* 1.13, $CHCl_3$); recrystallised from Et_2O–hexane, colourless needles, mp 59–60.5 °C, $[\alpha]_D^{21}$ −161.8 (*c* 0.22, $CHCl_3$)}.[3] On the other hand, the same mono-thiol diester **1** was treated with $AlCl_3$ (2.4 equiv.) in the presence of Et_3N (2.4 equiv.) in CH_2Cl_2 at 0 °C to afford cyclic β-keto thioester **8** as a colourless oil in 61% yield. Compound **8** was readily converted to the methyl ester (+)-**7** {97% ee,‡ $[\alpha]_D^{22}$ +155.7 (*c* 1.04, $CHCl_3$); recrystallised from Et_2O–hexane, colourless needles, mp 59.5–60 °C, $[\alpha]_D^{23}$ +158.7 (*c* 1.06, $CHCl_3$)} in a quantitative yield by transesterification with CF_3CO_2Ag (2 equiv.) in MeOH–THF (1 : 1) at room temperature.[4] Similar treatment of **1** in one-pot without isolation of **8** gave (+)-**7** {89% ee,‡ $[\alpha]_D^{24}$ +142.9 (*c* 1.20, $CHCl_3$); recrystallised from Et_2O–hexane, colourless needles, mp 59–60.5 °C, $[\alpha]_D^{22}$ +165.5 (*c* 1.05, $CHCl_3$)} in 72% yield from **1**.

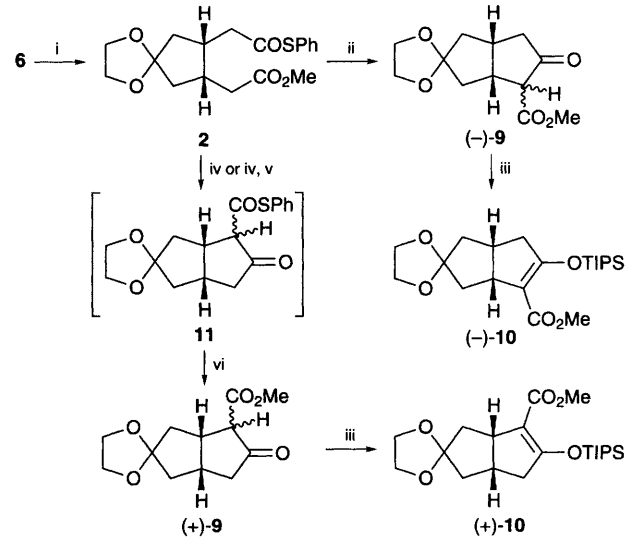
Subsequently, other enantiodivergent Dieckmann-type cyclisation reactions were attempted as shown in Scheme 3. The reaction of mono-thiol diester **2** with LDA (2.5 equiv.) and HMPA (1 equiv.) in THF at −50 °C furnished cyclic β-keto ester (−)-**9** {colourless oil, $[\alpha]_D^{22}$ −21.2 (*c* 1.05, $CHCl_3$)} as a mixture of the keto and enol forms in 44% yield. On treatment with $AlCl_3$ (3.6 equiv.) and Et_3N (3.6 equiv.) in CH_2Cl_2 followed by transesterification with K_2CO_3 (2 equiv.) in MeOH–CH_2Cl_2 (1 : 1), **2** was converted to (+)-**9** {colourless oil, $[\alpha]_D^{23}$ +23.6 (*c* 0.48, $CHCl_3$)} as a mixture of the keto and enol forms in 43% yield. In order to determine the enantiomeric purity of both compounds (−)-**9** and (+)-**9**, which were treated with triisopropylsilyl (TIPS) chloride (1.5 equiv.) in the



Scheme 1



Scheme 2 *Reagents and conditions*: i, CDI, PhSH, THF; ii, LDA, HMPA, THF; iii, $AlCl_3$, Et_3N, CH_2Cl_2; iv, CF_3CO_2Ag, MeOH–THF (1 : 1)



Scheme 3 *Reagents and conditions*: i, CDI, PhSH, THF; ii, LDA, HMPA, THF; iii, KH, TIPSCl, THF; iv, $AlCl_3$, Et_3N, CH_2Cl_2; v, gel filtration (Sephadex LH-20, THF); vi, K_2CO_3, MeOH–CH_2Cl_2 (1 : 1)

presence of excess KH in THF to give the corresponding TIPS enolates (−)-**10** {84% yield, 98% ee,§ colourless oil, $[\alpha]_D^{25}$ −19.8 (*c* 1.02, $CHCl_3$)} and (+)-**10** {79% yield, 83% ee,§ colourless oil, $[\alpha]_D^{22}$ +16.6 (*c* 1.12, $CHCl_3$)}, respectively. Although pure β-keto thioester **11** could not be isolated because of its instability on silica gel, similar treatment (transesterification followed by TIPS-enolisation) of the residue, obtained by gel filtration of crude **11** through a Sephadex LH-20 column, afforded higher enantiomeric excess of (+)-**10** {90% ee,§ $[\alpha]_D^{24}$ +19.2 (*c* 1.01, $CHCl_3$)} in 32% yield from **2**. Optically active compounds **7**, **9** and **10** should be useful for asymmetric syntheses of prostacarbacyclins,[3] biologically active sesquiterpenoids[5] and other natural products.[6]

Footnotes

† Determined by HPLC analysis of (4*S*)-isopropyl-1,3-thiazolidine-2-thione amide of the monocarboxylic acid.[2]

‡ Calculated on the basis of the specific rotation value of pure (−)-**7** {$[\alpha]_D^{23}$ −160.9 (*c* 0.21, $CHCl_3$)}.[3]

§ Determined by HPLC analysis (Daicel CHIRALPAK AD) with hexane–propan-2-ol (200 : 1).

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