

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

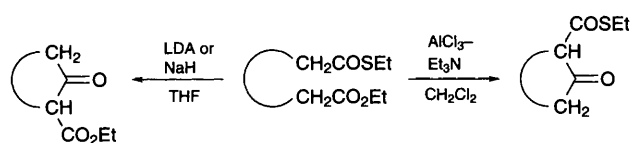
Shigeki Sano, Hideki Ushiroguchi, Kenji Morimoto, Satoshi Tamai and Yoshimitsu Nagao*

Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770, Japan

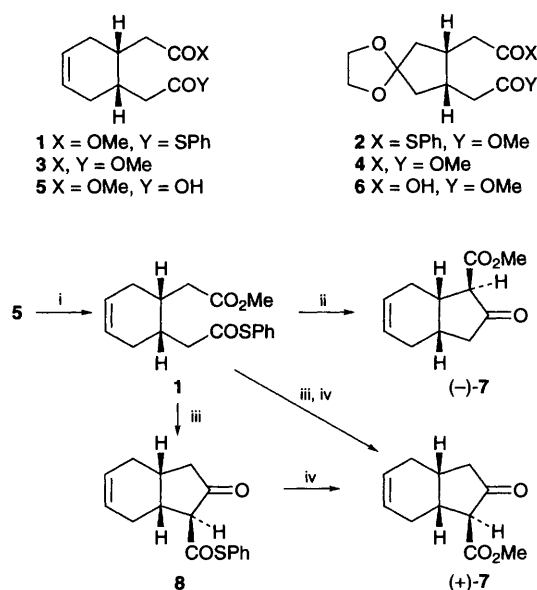
The chiral mono-thiol diester, **1** or **2**, is converted to the corresponding enantiomeric cyclised products, (–)-**7** and (+)-**7** or (–)-**9** and (+)-**9**, depending on whether LDA or $\text{AlCl}_3\text{-Et}_3\text{N}$ is used.

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 $\text{Sn}(\text{OSO}_2\text{CF}_3)_2$ in the presence of Et_3N or *N*-ethylpiperidine.¹ Among these Dieckmann-type reactions, the cyclisation mode of mono-thiol diesters employing $\text{AlCl}_3\text{-Et}_3\text{N}$ 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, $[\alpha]_{\text{D}}^{21} -4.5$ (c 0.69, CHCl_3)]³ and **2** [90% yield, colourless



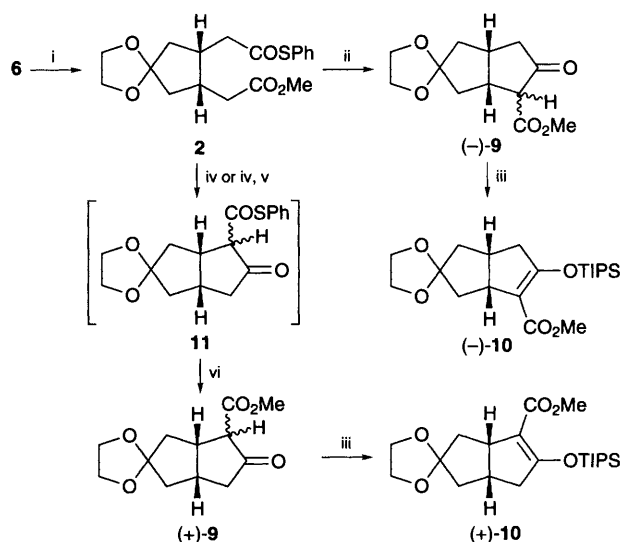
Scheme 1



Scheme 2 Reagents and conditions: i, CDI, PhSH, THF; ii, LDA, HMPA, THF; iii, AlCl_3 , Et_3N , CH_2Cl_2 ; iv, $\text{CF}_3\text{CO}_2\text{Ag}$, MeOH-THF (1 : 1)

needles ($\text{CH}_2\text{Cl}_2\text{-hexane}$), mp 64.5–65.5 °C, $[\alpha]_{\text{D}}^{23} +31.9$ (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, $[\alpha]_{\text{D}}^{27} -154.7$ (c 1.13, CHCl_3); recrystallised from $\text{Et}_2\text{O-hexane}$, colourless needles, mp 59–60.5 °C, $[\alpha]_{\text{D}}^{21} -161.8$ (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, $[\alpha]_{\text{D}}^{22} +155.7$ (c 1.04, CHCl_3); recrystallised from $\text{Et}_2\text{O-hexane}$, colourless needles, mp 59.5–60 °C, $[\alpha]_{\text{D}}^{23} +158.7$ (c 1.06, CHCl_3)] in a quantitative yield by transesterification with $\text{CF}_3\text{CO}_2\text{Ag}$ (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, $[\alpha]_{\text{D}}^{24} +142.9$ (c 1.20, CHCl_3); recrystallised from $\text{Et}_2\text{O-hexane}$, colourless needles, mp 59–60.5 °C, $[\alpha]_{\text{D}}^{22} +165.5$ (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, $[\alpha]_{\text{D}}^{22} -21.2$ (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 $\text{MeOH-CH}_2\text{Cl}_2$ (1 : 1), **2** was converted to (+)-**9** [colourless oil, $[\alpha]_{\text{D}}^{23} +23.6$ (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 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 , $\text{MeOH-CH}_2\text{Cl}_2$ (1 : 1)

presence of excess KH in THF to give the corresponding TIPS enolates (–)-**10** {84% yield, 98% ee, § colourless oil, $[\alpha]_{\text{D}}^{25}$ –19.8 (*c* 1.02, CHCl₃)} and (+)-**10** {79% yield, 83% ee, § colourless oil, $[\alpha]_{\text{D}}^{22}$ +16.6 (*c* 1.12, CHCl₃)}, 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, § $[\alpha]_{\text{D}}^{24}$ +19.2 (*c* 1.01, CHCl₃)} in 32% yield from **2**. Optically active compounds **7**, **9** and **10** should be useful for asymmetric syntheses of prostacarbacyclins,³ biologically active sesquiterpenoids⁵ 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** { $[\alpha]_{\text{D}}^{23}$ –160.9 (*c* 0.21, CHCl₃)}.³

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

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