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# Synthetic routes to the stereoisomers of 2,4-dimethylpentane-1,5-diol derivatives

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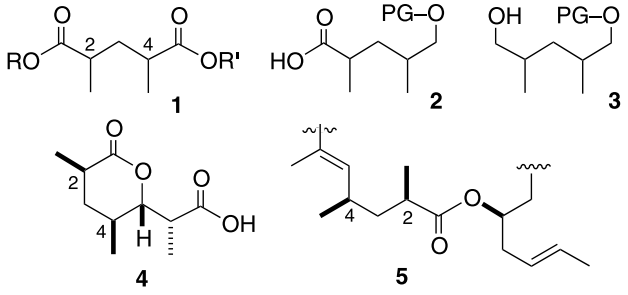
**Abstract**—Five different routes to every stereoisomer of non-symmetric derivatives of 2,4-dimethylpentanedioic acid and/or of *O*-monoprotected 2,4-dimethylpentane-1,5-diols, which are common building blocks for the total synthesis of many polypropionates, have been investigated. Alkylation of the lithium enolate of *N*-propanoylpseudoephedrine turned out to be the most appropriate method, in connection with the synthesis of fragment C1–C5 of amphidinolide K.


Access to stereoisomers of non-symmetric 2,4-dimethylglutaric acid esters **1**, and/or of related molecules with different oxygen functionalities at C1 and C5 such as **2** and **3**, has been a subject of continuous interest, since these compounds are appropriate building blocks for the synthesis of complex natural products, especially of macrolide-like antibiotics.[1] Prelog–Djerassi lactonic acid **4**[2] is a typical example of a substance that may be readily synthesised from precursors such as a suitable *syn*-**1** or (2*R*,4*S*)-**2**. Representative examples of natural product syntheses from stereoisomers of **1**–**3** are those of 6-deoxyerythronolide B,[3a] conglobatin,[3b,c] mycinolide V,[3d] the side chain of zaragozic acid A,[3e–g] siphonarienone,[3h] the antibiotic borrelidin,[3i] the aliphatic chain of microcolin B,[3j] salinomycin,[3k] α,γ-dimethyl γ- and δ-amino acids,[3l,m] a scyphostatin fragment,[3n] azaspiracid[3o,p] and supellapyrone.[3q]

In this context, we focussed our attention on the structure of (−)-amphidinolide K, a cytotoxic macrolide isolated by Kobayashi et al.,[4] the 'southern' part of which is **5**. The absolute configurations of the stereocentres at C2 and C4 were not immediately established.[4] Thus, we started a project[5] on the total synthesis of amphidinolide K and congeners beginning the preparation of samples of the four possible C1–C5 substructures.[6] We explain here all the approaches that we investigated to reach both enantiomers of *syn* isomers **1**–**3** and both *anti* enantiomers, with the hope that our results will save time for researchers who face similar problems in the future.




Separation and resolution of the commercially available *meso*/*dl* mixture of 2,4-dimethylglutaric acids[7] was first considered. After dehydration of 2,4-dimethylglutaric acids by heating with acetic anhydride, *meso*-glutaric anhydride (**6**) could be separated after several crystallisations from ethyl acetate, the mother liquors containing mainly racemic anhydride. Asymmetrisation of the *meso* isomer by treatment with (*R*)-1-phenylethylamine, reduction of the carboxyl group with borane, separation of the diastereomeric monoamides (**7** and **7′**) by crystallisation (with purification by flash column chromatography), and hydrolysis of the amide group (with cyclisation) afforded the corresponding enantiomeric lactones (**8** and *ent*-**8**, respectively).[8] However, we found that the overall process was cumbersome, as it requires several crystallisations, and did not allow one to obtain pure *anti* stereoisomers.[9]

*Keywords*: alkylation; asymmetric synthesis; diastereoselection; enolates; macrolides; Michael reactions.
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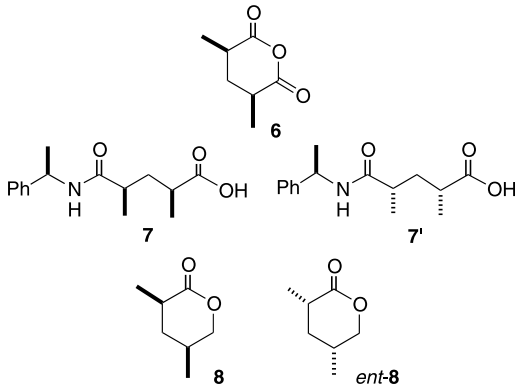
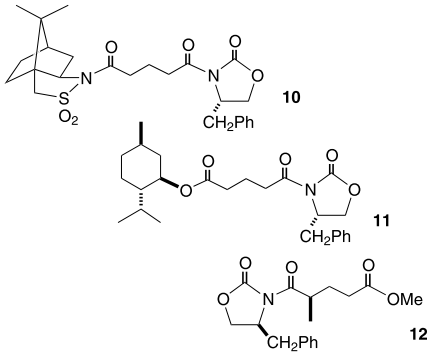


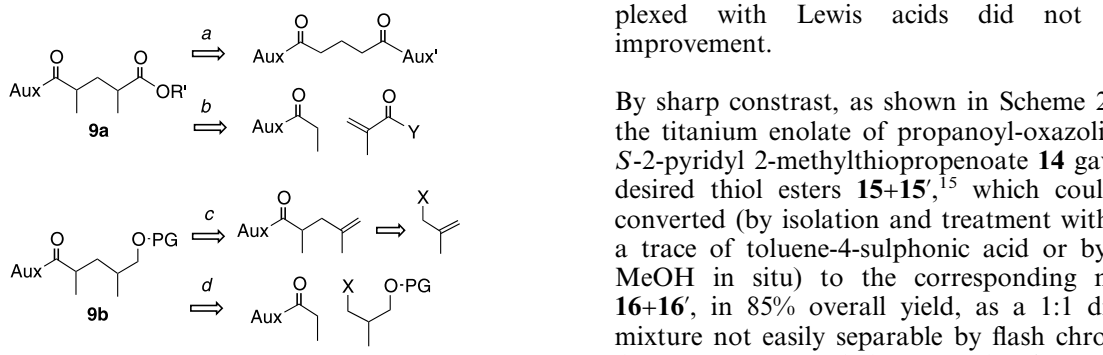
A simple retrosynthetic analysis of structures **9a**,**b** (related to **1**–**3**) affords a plethora of possible routes, four of which (those indicated in Scheme 1, where Aux represents a suitable chiral auxiliary) were investigated in this work. The aldol-like reaction between Aux-CO-Et and OHC-CHMe-$CH_2O$-PG was not contemplated; it is a well-known method,[10] but it requires two additional steps for the removal of the central hydroxy group.

**Attempted asymmetric double methylation of pentanedioic acid derivatives** (Scheme 1, route a). From glutaric anhydride we prepared derivatives **10** and **11**,[11] which were treated with an excess of base and methylating agent. For the sake of comparison, methylation of **12**, prepared by Michael addition of the corresponding *N*-propanoyloxazolidinone to methyl acrylate,[12] was also attempted under similar conditions.[13] In practice, all the experiments performed with **10** and **11**, using two or more equiv. of LDA or NaHMDS (either added from the beginning or in two steps) and a large excess of methyl iodide or methyl triflate, in THF at different temperatures, led to complex mixtures which did not contain the desired dimethylated product. In the case of **10**, the major product appeared to be that methylated at the position α to the oxazolidinone moiety,[14] with recovery of starting material and the camphorsultam auxiliary after the workup. In the presence of HMPA, which is usually required to perform alkylations of enolates of *N*-acyl derivatives of the camphorsultam,[11a] we did not detect any dimethylated product either. In the case of **11**, our best result was a 67% yield of the product methylated at the position α to the oxazolidinone moiety (by using >2 equiv. of NaHMDS and methyl iodide) and a 25% yield of the partially hydrolysed starting material. Treatment of **12** with either LDA or NaHMDS (1.1 equiv.) and then with either methyl iodide or methyl triflate did not yield the desired dimethylated product.

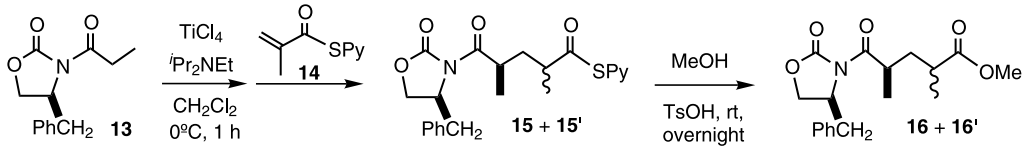


**Asymmetric Michael addition to methacrylates** (Scheme 1, route b). Reaction of titanium enolates of chiral *N*-propanoyl-2-oxazolidinones with ethyl acrylate or acrylonitrile had been reported to afford conjugate adducts in excellent yields and diastereoselectivities (>99% de),[12] which we confirmed in our lab. However, less reactive Michael acceptors such as 2-methylpropenoate (methacrylate) derivatives did not react; changes in temperature, solvent, enolisation conditions and addition of methyl methacrylate previously complexed with Lewis acids did not afford any improvement.

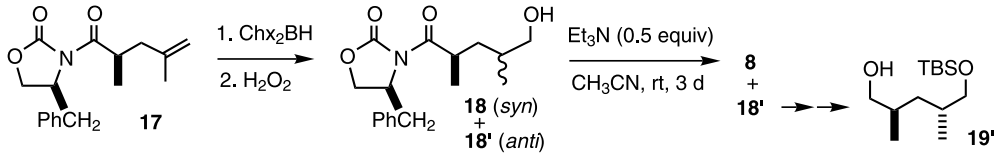
By sharp constrast, as shown in Scheme 2, reaction of the titanium enolate of propanoyl-oxazolidone **13** and *S*-2-pyridyl 2-methylthiopropenoate **14** gave rise to the desired thiol esters **15**+**15′**,[15] which could be readily converted (by isolation and treatment with MeOH and a trace of toluene-4-sulphonic acid or by addition of MeOH in situ) to the corresponding methyl esters **16**+**16′**, in 85% overall yield, as a 1:1 diastereomeric mixture not easily separable by flash chromatography. Attempts to control the stereochemistry of the methyl group at Cγ by using (−)-sparteine instead of ethyldiisopropylamine in the enolisation step or by quenching the



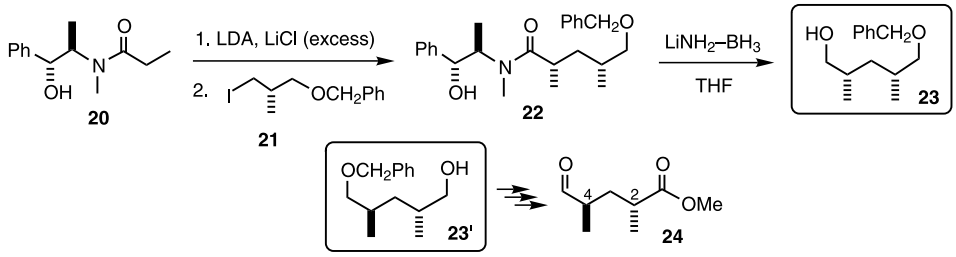
**Scheme 1.**



**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

reaction at −78°C with chiral aminoalcohols such as quinine and (−)-*N*-methylephedrine before the addition of MeOH, were unsuccessful, as only modest improvements in the diastereoselection were noted. This is a drawback of the approach, despite the fact that the performance of **14** is an encouraging result.

**Reaction of a chiral enolate with 3-bromo-2-methylpropene followed by hydroboration and oxidation** (Scheme 1, route c).[16] The sodium enolate of **13** and 3-bromo-2-methylpropene afforded the allylation product **17**, which was treated with different achiral and chiral boranes ($BH_3$–$Me_2S$, 9-BBN, catecholborane/$(Ph_3P)_3RhCl$, thexylborane, dicyclohexylborane, diisopinocampheylborane, isopinocampheylborane) followed by oxidation ($H_2O_2$/NaOH, $H_2O_2$/$NaHCO_3$, $H_2O_2$/$NaHCO_3$/glycerol) to afford diastereomeric alcohols **18** (*syn*) and **18′** (*anti*). The best isolated yield (82% overall yield) was obtained using an excess of $Chx_2BH$ and oxidising the C–B bonds in the presence of glycerol, but no significant asymmetric induction was detected. On the other hand, moderate enrichment in **18** was achieved with thexylborane, but the yields were poor. The remaining experiments afforded worse results (yields and diastereoselectivities). Separation of **18** and **18′** by flash chromatography or by MPLC was not feasible, but we took advantage of the easier cyclisation of the *syn*-dimethyl derivative **18** into lactone **8**,[17] in $Et_3N/CH_3CN$, to isolate the *anti* diastereomer (**18′**), which was protected as its *tert*-butyldimethylsilyl ether (TBSCl, imidazole, $CH_2Cl_2$, 85%) and reduced ($LiBH_4$, MeOH, THF, 98%) to enantiopure **19′** (Scheme 3). The diastereomeric ratio of **19′** (*anti*) to **19** (*syn* isomer, not depicted) was shown by GC to be 95:5.

Analogously, *ent*-**19′** and *ent*-**8** were prepared starting from *ent*-**13**, via *ent*-**17**. Thus, pure *anti* isomers **19′** and *ent*-**19′** can be obtained by appropriate allylation and hydroboration reactions. Pure *syn* isomers **8** and *ent*-**8** can be prepared via the same process (an alternative to the above-mentioned procedure from *meso*-glutaric anhydride).

**Asymmetric alkylation of *N*-propanoylpseudoephedrine enolates with *O*-benzyl-3-iodo-2-methylpropan-1-ol** (Scheme 1, route d). Myers et al. reported the use of pseudoephedrine as a practical chiral auxiliary for the alkylation of the corresponding amide enolates.[18a,b] Standard, non-activated alkyl iodides, which do not react with enolates of imides (i.e. when the N atom is linked to a second EWG), react efficiently with pseudoephedrine amides such as **20**. The alkylating agent required by us, (*S*)-3-iodo-2-methylpropan-1-ol, protected as its benzyl ether **21**,[19] was prepared from methyl (*S*)-3-hydroxy-2-methylpropanoate.[20] Reaction of the lithium enolate of **20** with **21** (see Scheme 4) in THF at rt afforded, in 87% yield and with a ≥99% de, the *syn*-dimethyl derivative **22**, which was quantitatively reduced with lithium amidotrihydroborate[18] to the *syn*-dimethyl alcohol **23**.

By using (1*S*,2*S*)-pseudoephedrine derivative (*ent*-**20**) and **21**, the *anti*-dimethyl alcohol **23′** was similarly prepared, also in excellent overall yield. Compounds **23** and **23′**,[21,22] by suitable manipulations, can afford every stereoisomer of each substructural unit **1**–**3**.[23] Alcohol **23′** is synthetically equivalent to **24**, the C1–C5 synthon or building block required in our total synthesis of (−)-amphidinolide K.[5]

In summary, among the five chemical methods of obtaining the set of enantiopure fragments of type **1**–**3** (2,4-dimethylpentanedioates, 2,4-dimethylpentane-1,5-diols, etc.) investigated by us, the alkylation of pseudoephedrine-derived amides[18] turned out to be the most appropriate procedure.

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Professor David A. Evans (Merendero de la Mari, Barcelona, January 1998) regarding asymmetric Michael reactions studied in this work are also acknowledged. J.V. dedicates this work to Prof. Enrique Meléndez (Universidad de Zaragoza) and Prof. Marcial Moreno (Universitat Autònoma).

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14. The $^1$H NMR signal at $\delta$ 3.01 (t, $J=7.2$, 2H), corresponding to the $CH_2CO$ group linked to Evans' auxiliary of the starting material (**10**), was shifted to $\delta$ 3.80–3.72 (m, 1H) in the methylation product, whereas the signal at 2.84 (t, $J=7.2$, 2H), due to the $CH_2CO$ group linked to Oppolzer's auxiliary, remained. Only one new methyl signal appeared, at 1.25 ppm (d, $J=6.9$, 3H). Comparison of the $^{13}$C NMR spectra and MS corroborated that the major compound was the monomethylated product.

15. It is worth noting that (i) *S*-phenyl and *S*-4-pyridyl thiomethacrylates did not react under identical conditions and that (ii) when *S*-2-pyridyl methacrylate was previously complexed with a second equiv. of $TiCl_4$, all the starting material was recovered. It suggests that coordination of the pyridine nitrogen atom to the titanium atom of the enolate (or its chelation by *N* and *O* of the thiol ester) is the key point.
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20. We prepared **21** in four simple high-yielding steps, as follows (Ref. 5): protection of the hydroxy group of commercially available methyl (*S*)-3-hydroxy-2-methylpropanoate with benzyl 2,2,2-trichloroacetidimidate and $Me_3SiOTf$; reduction of the ester group with an excess of $^{i}Bu_2AlH$; activation of the hydroxy group as its mesylate; and treatment with NaI in acetone. Also see Ref. 19. These four steps can be shortened to three if a direct iodo–dehydroxylation reaction is utilised (cf. Larock, R. C. *Comprehensive Organic Transformations*; Wiley: New York, 1999, pp 696–697).
21. Compound **23**: oil; $R_f$ (3:1 $CH_2Cl_2$–EtOAc) 0.61; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 7.33 (br s, 5H), 4.50 (s, 2H), 3.50–3.40 (m, 2H), 3.30–3.20 (m, 2H), 1.92–1.82 (m, 1H), 1.75–1.63 (m, 1H), 1.52–1.40 (m, 2H), 0.96 (d, $J=6.6$, 3H), 0.93 (d, $J=6.6$, 3H); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 138.5, 128.3, 127.5, 127.4, 75.8, 73.0, 68.0, 37.6, 33.2, 31.0, 18.1, 17.5; GC (SE-30, 50°C 1 min, 4°C/min→250°C 10 min) $t_r=27.42$ min, $t_r$ (minor diast.)=26.98 min, diastereomeric ratio=98:2. Compound **23′**: oil; $R_f$ (3:1 $CH_2Cl_2$–EtOAc) 0.60; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 7.33 (br s, 5H), 4.50 (s, 2H), 3.49–3.37 (m, 2H), 3.33–3.24 (m, 2H), 1.94–1.82 (m, 1H), 1.80–1.71 (m, 1H), 1.29–1.18 (m, 2H), 0.91 (d, $J=6.7$, 3H), 0.89 (d, $J=6.7$, 3H); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz) $\delta$ 138.5, 128.3, 127.5, 127.4, 76.6, 73.0, 68.8, 37.2, 33.0, 30.5, 16.9, 16.3; CIMS ($NH_4^+$) $m/z$ 240 (M+18, 100), 223 (M+1, 53); GC (50°C 1 min, 4°C/min→250°C 10 min) $t_r=27.01$ min, $t_r$ (minor diast.)=27.40 min, diastereomeric ratio=98:2.
22. These compounds are known: (a) Hale, M. R.; Hoveyda, A. H. *J. Org. Chem*. **1992**, *57*, 1643–1645; (b) Sefkow, M.; Neidlein, A.; Sommerfeld, T.; Sternfeld, F.; Maestro, M. A.; Seebach, D. *Liebigs Ann. Chem*. **1994**, 719–729; (c) Abiko, A.; Moriya, O.; Filla, S. A.; Masamune, S. *Angew. Chem., Int. Ed*. **1995**, *34*, 793–795.
23. Alternatively, the use of *ent*-**21** would give the enantiomers of the compounds shown in Scheme 4.