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Allylic strain effects on the stereochemistry of the alkylation reaction of mycophenolic acid chiral enolates

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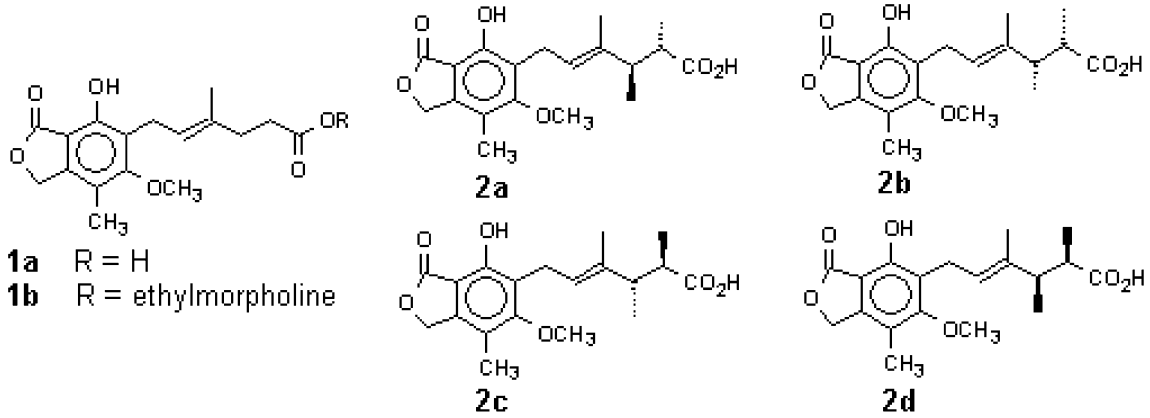
Abstract—An attempted enantioselective synthesis of all the four individual diastereomers of α,β-dimethylated mycophenolic acid using Evans chiral auxiliaries is reported. The 1,3-allylic strain effect on the enolates used favor the formation of the *syn* acids.

Mycophenolic acid **1a** and mycophenolate mofetil **1b** (Scheme 1) are two very potent inhibitors of inosine-5′-monophosphate dehydrogenase (IMPDH),[1] a key enzyme involved in the de novo biosynthesis of guanine derived nucleotides, properties that confer them a wide spectrum of biological activity.[2] Mycophenolate mofetil is now known by the brand name of CellCept (Hoffmann LaRoche) and was approved in 1995 by the FDA for prevention of rejection in renal allograft patients and in 1998 for use in heart transplant procedures.

Within the context of a previous medicinal chemistry program[3] whose main goal was to establish the structure–activity relationship of some alkylated analogs of **1a**, we became interested in the synthesis of all the four individual diastereomers **2a–d** of α,β-dimethylated mycophenolic acid in very high optical purity. Since a large number of derivatives of mycophenolic acid such as the β-methylated compound **3** are readily available[4] from **1a** itself, we envisioned a strategy in which compound **4** (Scheme 2), prepared from **3** following literature procedures,[5] would be an ideal starting material for our synthetic plan. The well established Evans protocol[6] for the alkylation of chiral oxazolidinones such as **4** appealed to us as suitable for introducing the methyl group and for controlling the stereochemistry at the α-stereocenter on **4** with the proper choice of the (*S*) or (*R*) oxazolidinone chiral auxiliaries. On the other hand, the stereochemistries of the β-stereocenters could be set by the resolution of **4**.



Scheme 1.

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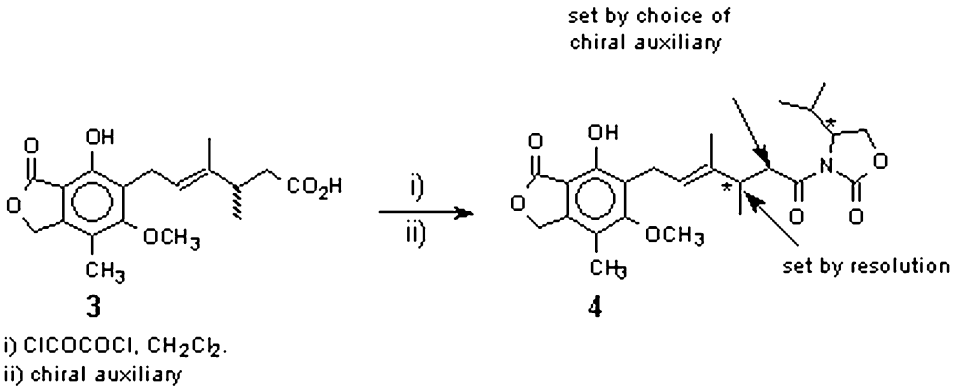
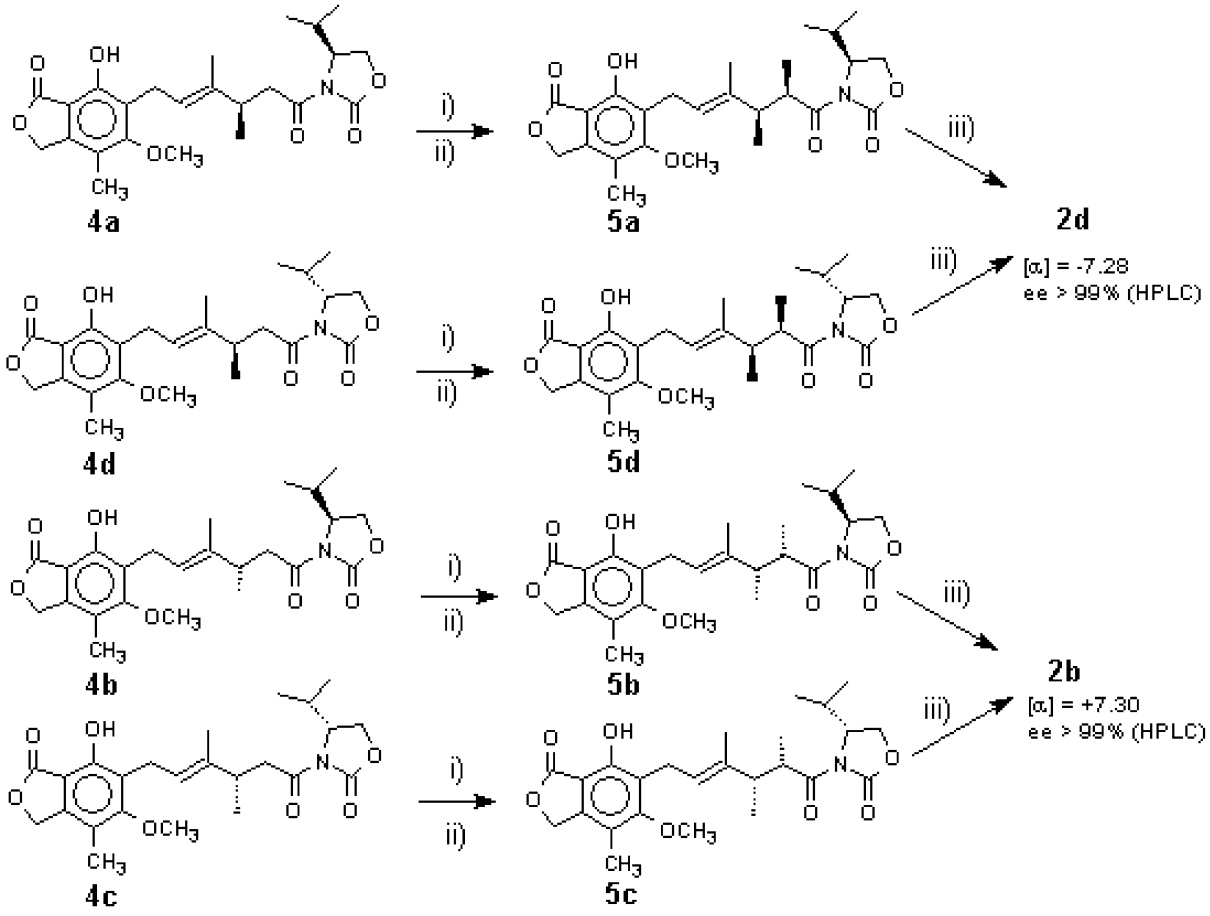


Scheme 2.

Therefore, the lithium salt of (4*S*)-(−)-4-isopropyl-2-oxazolidinone was reacted with the acid chloride of racemic **3** to give a mixture of diastereoisomers **4a** and **4b** (Scheme 3) in 68% yield. The mixture was easily separated in column chromatography (silica gel) to afford pure **4a** and **4b**. Following the same sequence, the lithium salt of (4*R*)-(+)-4-isopropyl-2-oxazolidinone yielded pure **4c** and **4d** as white solids. The stereochemical assignment at the β-stereocenter of molecules **4a**–**d** is based on the X-ray crystal structure of **4a** (Fig. 1) in which the *R* configuration of the methyl group at this carbon can be seen. Therefore, it was expected that alkylation of **4a** and **4c** followed by removal of the chiral auxiliary would provide the *anti* acids **2a** and **2c** whereas **4b** and **4d** the *syn* acids **2b** and **2d**. In fact, Hruby and co-workers[7] utilized a similar strategy in the synthesis of the four enantiomers of β-methylphenyl alanine. Thus, when diastereoisomers **4b** and **4d** were treated with 2.2 equivalents of NaHDMS[8] in THF at −78°C, followed by the addition of iodomethane at −50°C during 6 hours, the alkylated products **5b** and **5d**



Scheme 3. (i) NaHOMS, THF, −78°C, (ii) CH_3I, −50°C, (iii) LiOH, H_2O_2 (30%), THF-H_2O.

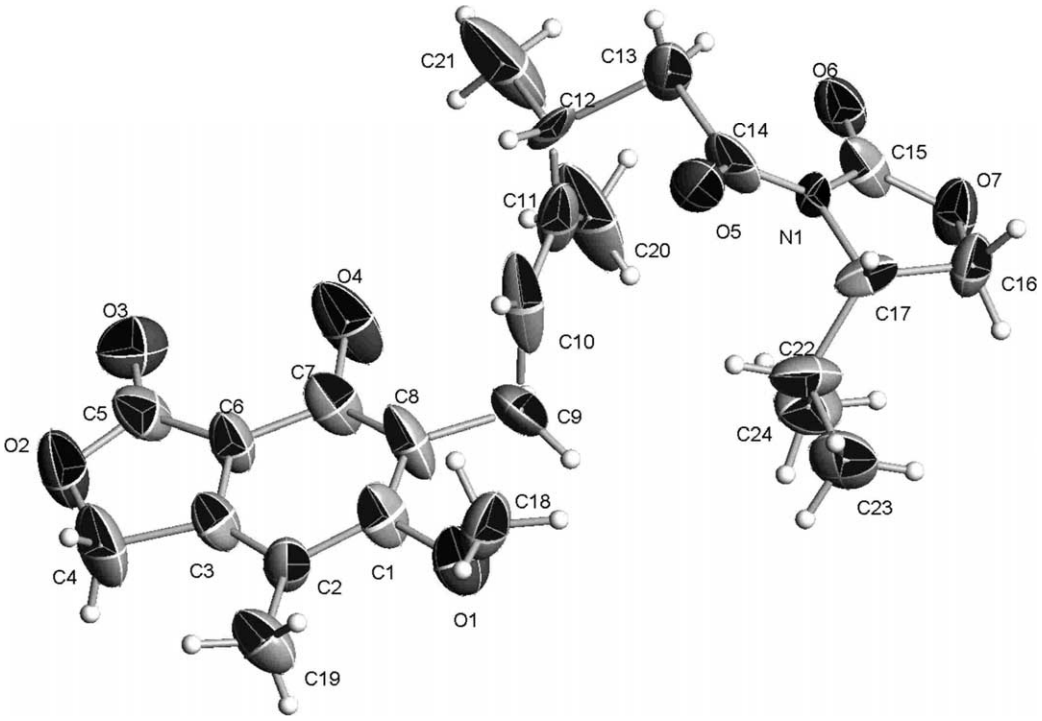


Figure 1. X-Ray structure of **4a**.

were obtained in 60–65% yield (de>96%, NMR). To establish that the asymmetric induction occurred as desired, **5b** was further purified by recrystallization from dichloromethane and hexane and submitted for X-ray analysis. Fig. 2 shows the X-ray crystal structure of **5b** showing the predicted stereochemistry at the newly formed chiral centers. Removal of the chiral auxiliaries with lithium peroxide yielded the *syn* acids **2b** and **2d** in 60–70% (ee >99%, chiral HPLC).[9]

When we attempted to prepare the *anti* enantiomers **2a** and **2c** following the same procedure, we observed that the alkylation reaction was much slower (12 h), affording the alkylated products **5a** and **5c** in lower yields (30–35% over 50% recovered starting material). Removal of the chiral auxiliary yielded two acids whose NMR, optical rotation and retention time on chiral HPLC were identical to the *syn* acids obtained from **4b** and **4d**. Formation of the *anti* acids **2a** and **2c** could not be detected in this sequence of reactions.

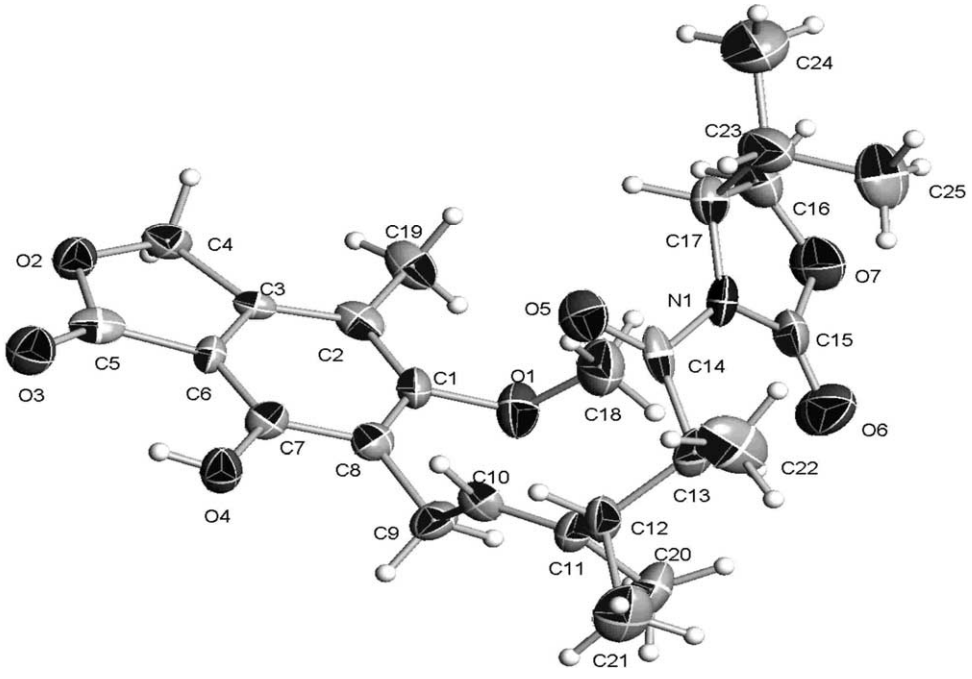
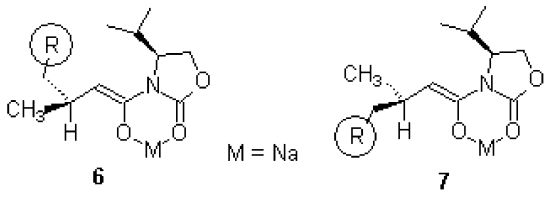


Figure 2. X-Ray structure of **5b**.



Scheme 4.

We believe this stereochemical behavior can be explained in terms of the 1,3-allylic strain effects[10] on the enolates generated from molecules **4a**–**d**. For example, the preferred conformations of the enolates generated from **4a** and **4b** could be represented by **6** and **7** (Scheme 4). In both structures **6** and **7** the *si*-face of the enolate is shielded by the isopropyl group.

However, in conformation **6**, the R chain is displaced toward the back of the plane of the enolate moiety shielding more effectively the *re*-face and thus favoring the reaction with iodomethane from the *si*-face. This is consistent with our experimental observation that enolate **6** is less reactive than enolate **7**.

We have NMR evidence that **4a** is a bent molecule even before the enolization process since a strong NOE effect is observed between the phenolic proton and the methyl group attached to the double bond on the side chain. In conclusion, we suggest that the 1,3-allylic strain effect plays a key role in the stereochemical behavior of these reactions. We are performing further studies, including theoretical calculations, to determine the most probable conformations of these enolates in order to evaluate the scope of the 1,3-allylic strain effects in related molecules.

Acknowledgements

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