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Preparation of Pyrrolidine-Based PDE4 Inhibitors via Enantioselective Conjugate Addition of α-Substituted Malonates to Aromatic Nitroalkenes

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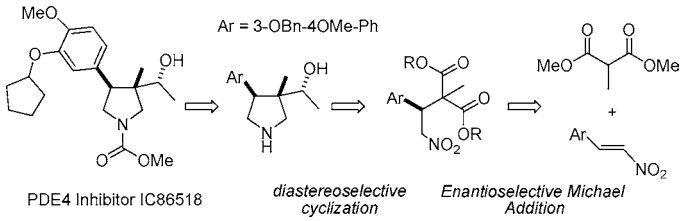
ABSTRACT



The enantioselective conjugate addition of α-substituted malonates to aromatic nitroalkenes generates a stereocenter at the carbon bearing the aromatic group and an adjacent prochiral center from the α-substituted malonate. Nitro reduction followed by diastereoselective cyclization provides pyrrolidinones with two contiguous stereocenters, one of which is quaternary. This sequence was used for the preparation of the PDE4 inhibitor IC86518. Additional examples of the enantioselective Michael addition illustrate the scope of the reaction.

In recent years, phosphodiesterase type 4 (PDE4), a cyclic adensosine monophosphate (cAMP)-specific enzyme, has become an important medicinal target.[1] Inhibition of PDE4 has been shown to lower the inflammatory response in a variety of pro-inflammatory cells.[2] Unfortunately, early clinical candidates suffered from undesired side effects, including nausea and emesis.[1] Over the course of a medicinal chemistry program targeting PDE4, a number of highly potent, nonemetic, selective PDE4 inhibitors were developed.[3] The pyrrolidine IC86518 (Figure 1) is a potent inhibitor of PDE4 (IC_{50} = 14 nm), and only the stereoisomer shown significantly reduced undesired emetic side effects in animal models. IC86518 was one of a number of *N*-substituted pyrrolidines that were prepared from the common intermediate **1** (Figure 1).

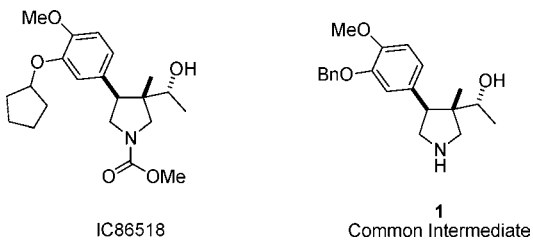


Figure 1. PDE4 inhibitor IC86518 and desired intermediate.

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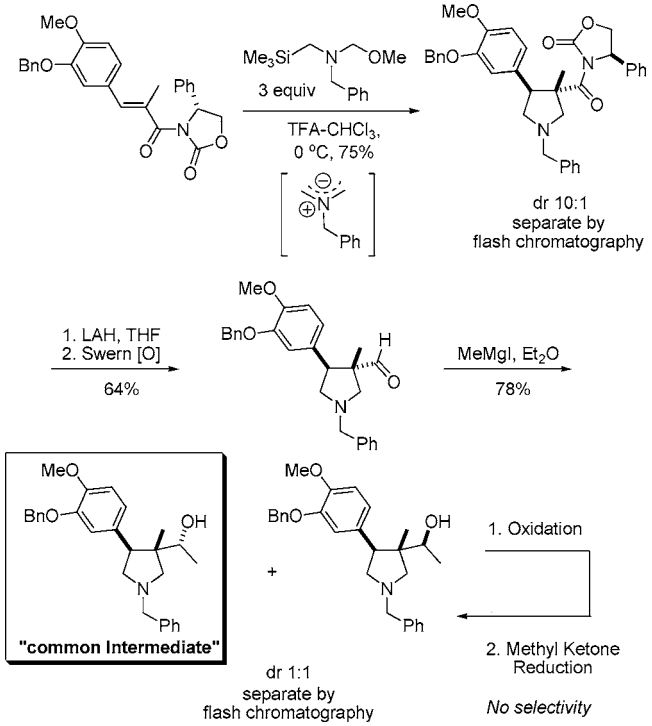
Compound **1** is a challenging synthetic target containing three contiguous stereocenters, one of which is a quaternary carbon bearing four carbon-based substituents. The preparation of quaternary carbon stereocenters continues to be a significant challenge for synthetic chemists and is an active area of research.[4] Initially, a 3 + 2 cycloaddition approach was used to access compound **1** (Scheme 1). While the

Scheme 1. Initial Synthesis of the Common Intermediate Core

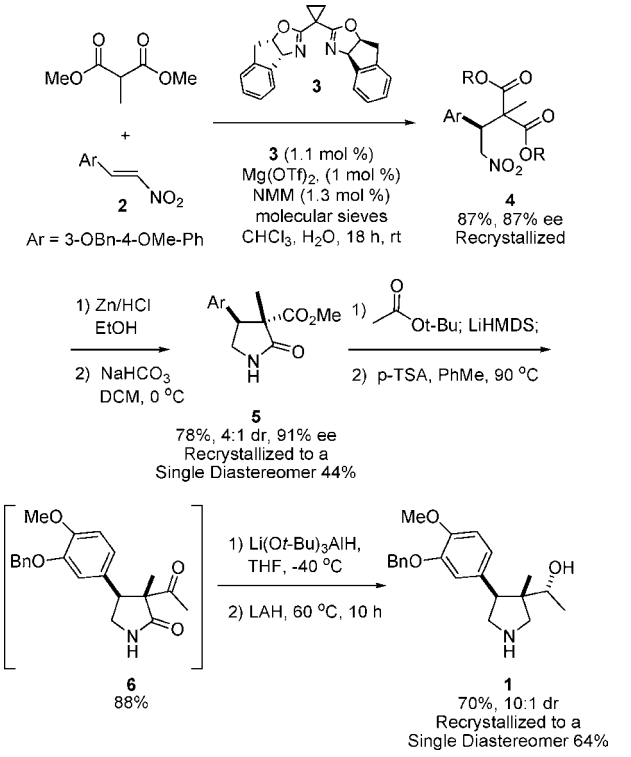


preparation of the quaternary center was stereoselective, the generation of the requisite secondary alcohol, either via the addition of MeMgI to the intermediate aldehyde, or by reduction of the correseponding methyl ketone, was not. Faced with multiple selectivity issues and the potential requirement of chromatography on scale, an alternative synthetic strategy based on the preparation of lactam **6** was investigated.

The asymmetric conjugate addition[5] of 1,3-dicarbonyl compounds to nitroalkenes has been reported using both metal-[6] and organocatalysis.[7] In the work of Ji and coworkers,[6a] the known bis(oxazoline) ligand **3**[8] was used in the presence of $Mg(OTf)_2$ and *N*-methylmorpholine (NMM) to provide enantiomerically enriched addition products in high yields. In this report and in the process patent that followed, there was no discussion of the application of this method to α-substituted malonates.[9] Subsequently, a full paper describing this method reported four examples of α-substituted malonates, three of which gave low enantioselectivities, including the methyl-substituted malonate required for the synthesis of intermediate **1**.[10] In this paper, we describe the synthesis of **1** and its conversion to IC86518 via the Michael addition of α-substituted malonates to aromatic nitroalkenes in high yields and enantiomeric excess.

The current synthesis of the common intermediate **1** is illustrated in Scheme 2. The enantioselective Michael addition between nitrostyrene **2** and dimethyl methylmalonate gave crude compound **4** in 86% ee. Recrystallization provided pure material in 87% yield with 87% ee on a 4 kg

Scheme 2. Synthesis of Common Intermediate **1**



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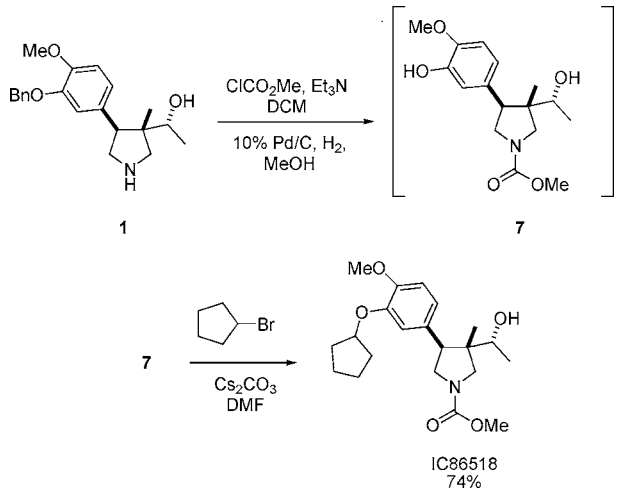
scale. A zinc-mediated nitro reduction of compound **4** followed by addition of a $NaHCO_3$ solution at 0 °C promoted cyclization and gave pyrrolidinone **5** with a 4:1 preference for the desired diastereomer. Fortuitously, recrystallization of the mixture from *tert*-butyl methyl ether provided the desired diastereomer in 44% yield and 91% ee. While the low yield can be attributed to the modest selectivity of the cyclization and difficulties in isolation, subsequent research showed that cyclization on the corresponding diethyl methylmalonate substrate provided diastereoselectivities greater than 10:1.[11] Conversion of methyl ester **5** to methyl ketone **6** was accomplished via a two-step procedure in which the enolate of *tert*-butyl acetate was condensed with the methyl ester followed by acid-catalyzed decarboxylation. Following an extractive workup and a solvent switch from toluene to THF, ketone **6** was selectively reduced (10:1 dr) with lithium tri-*tert*-butoxyaluminum hydride at −40 °C. The sense of asymmetric induction observed for the reduction is consistent with chelation control. Upon completion of the ketone reduction, lithium aluminum hydride (LAH) was added in situ and the mixture was heated to 60 °C for 15 h to provide common intermediate **1**. Subsequent recrystallization from isopropyl acetate gave a single diastereomer in 64% yield from **6**.[12] Over 1 kg of compound **1** was prepared by this route. The relative and absolute stereochemistry of **1** was confirmed by NMR and X-ray crystallography.

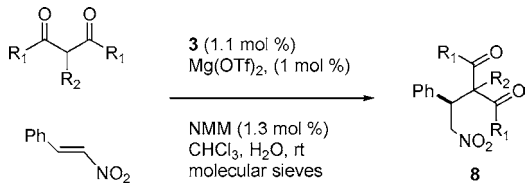
Intermediate **1** was readily converted to IC86518 in three steps (Scheme 3). Carbamate formation with methyl chloroformate followed by benzyl deprotection (H_2, Pd/C) gave the crude phenol **7**. Alkylation with cyclopentyl bromide provided IC86518 in 74% overall yield for the three steps.

Scheme 3. Synthesis of IC86518 from Common Intermediate **1**



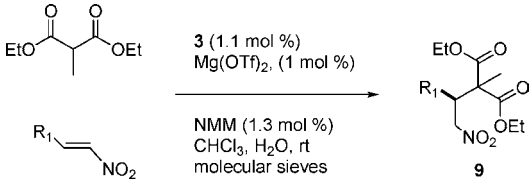
Due to the high efficiency and selectivity observed in the synthesis of compound **1**, we began to examine the scope of the α-substituted malonate addition. In the disclosure that reports the use of α-substituted malonates, morpholine was used as the base with a 5 mol % catalyst loading. In this report, the authors claim the reaction was sluggish and gave low ee's in all but one case.[10] In contrast, we found this reaction to be selective over a variety of α-substituted malonates (Table 1). For entries 1−4 (Table 1) (substrates previously reported), we observed higher yields and selectivities in all cases. In particular, the 93% ee shown in entry 1 is substantially higher than the 46% ee previously disclosed for this substrate.[10] Our results suggest that this reaction can tolerate a number of different substituents on the malonate including amines, ethers, halogens, and allyl groups (Table 1). While the reaction seems to be limited to aromatic nitroalkenes, functionally substituted aromatic groups are well tolerated (Table 2). Aromatic nitroalkenes containing ortho substitution were extremely selective in the cases

Table 1. Scope of the Malonate Michael Addition



entry	R_1	R_2	time (h)	adduct	yield (%)	ee (%)
1	OEt	Me	16	**8a**	99	93
2	OEt	NHBoc	19	**8b**	90	65
3	OMe	OMe	24	**8c**	88	90
4	OEt	NHAc	17	**8d**	75	44
5	OEt	Allyl	45	**8e**	72	82
6	OEt	Cl	18	**8f**	84	99
7	OEt	F	64	**8g**	85	94
8	OEt	Ph	48	**8h**	NR	NR

Table 2. Scope of the Malonate Michael Addition



entry	R_1	time (h)	adduct	yield (%)	ee (%)
1	2-furyl	18	**9a**	92	92
2	2-thiophenyl	21	**9b**	99	92
3	4-BrPh	21	**9c**	96	94
4	2-NO_2Ph	19	**9d**	92	99
5	4-OCF_3Ph	20	**9e**	66	93
6	3-CF_3Ph	45	**9f**	86	90
7	2-CF_3Ph	67	**9g**	77	98

(11) Investigations regarding the scope and limitations of the reduction/diastereotopic group selective cyclization step are ongoing and will be disclosed in due course.

(12) The final ee of compound **1** was found to be >99% following chiral derivatization and comparison to authentic, racemic samples which were derivatized and separated independently.

examined (entries 4 and 7, Table 2). We have found that toluene may be used as solvent in these reactions without loss of ee. For the reaction shown in Table 1, entry 1, substitution of toluene for chloroform gave 96% ee in 74% yield. Increasing the catalyst loading to 5 mol % was observed to decrease reaction time from 16 to 3 h for the substrate shown in Table 1, entry 1.[13]

In conclusion, we have demonstrated an enantioselective Michael addition of α-substituted malonates to nitrostyrenes. Addition products can be reduced and then cyclized selectively to give substituted pyrrolidinones containing contiguous stereocenters, one of which is quaternary. Yields and selectivities range from moderate to excellent. The method has been demonstrated to be applicable to a variety of substituted malonates and has been executed on kilogram scale in the synthesis of the PDE4 inhibitor IC86518.

(13) In our hands, using the conditions reported by the Barnes, Ji, and co-workers[10] for entry 1 of Table 1 provided **8a** in 39% yield and 90% ee in 6 h, which was in contrast to the published report (71% yield, 46% ee, 44 h). We found that using morpholine as a base gave significantly lower yields over catalyst loadings ranging from 1 to 5% as compared with NMM.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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