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Organocatalytic Asymmetric Total Synthesis of (*R*)-Rolipram and Formal Synthesis of (3*S*,4*R*)-Paroxetine

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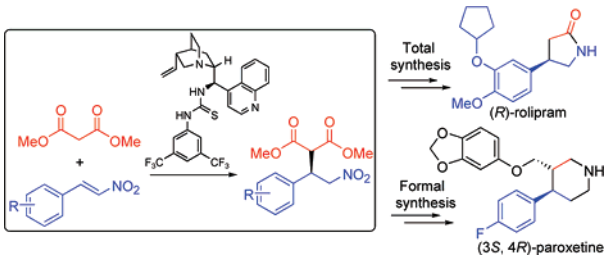
ABSTRACT



An efficient enantioselective total synthesis of (*R*)-rolipram and an efficient enantioselective formal synthesis of (3*S*,4*R*)-paroxetine has been achieved using the highly enantioselective Michael addition of malonate nucleophiles as key steps in both cases.

The highly enantioselective Michael addition of malonate nucleophiles to nitro olefins catalyzed by a bifunctional Lewis base, Brønsted acid organocatalyst derived from 9-amino(9-deoxy) epicinchonine has recently been reported.[1,2] This reaction provides direct access to β-substituted γ-nitro carboxylic acid derivatives, compounds rich in synthetic potential. In this paper we wish to demonstrate the synthetic power of this Michael addition reaction by employing it as the key step in both the total asymmetric synthesis of antidepressant (*R*)-rolipram[3] **1** and the formal asymmetric synthesis of (3*S*,4*R*)-paroxetine **2**, a selective serotonin reuptake inhibitor (SSRI) used in the treatment of depression.[4]

Although the transformation of an appropriate Michael adduct **5** to (*R*)-rolipram is tactically straightforward owing to its γ-amino acid backbone,[5] the analogous transformation to (3*S*,4*R*)-paroxetine, which requires a one carbon homologation, is not at first obvious.[4,6] However, we believed an

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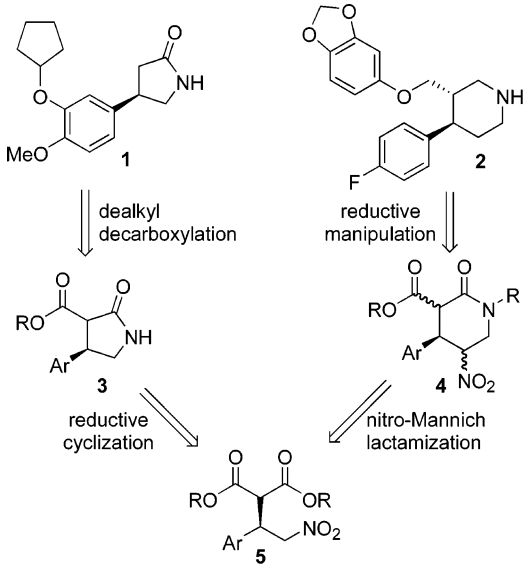
effective route could exploit the natural reactivity of nitro alkanes toward imines (the nitro-Mannich reaction) followed by an intramolecular cyclization to the δ-lactam **4**.[7] This would provide the core; the remainder of the synthesis would require reductive manipulation of nitro, amide, and ester functionalites (Scheme 1).

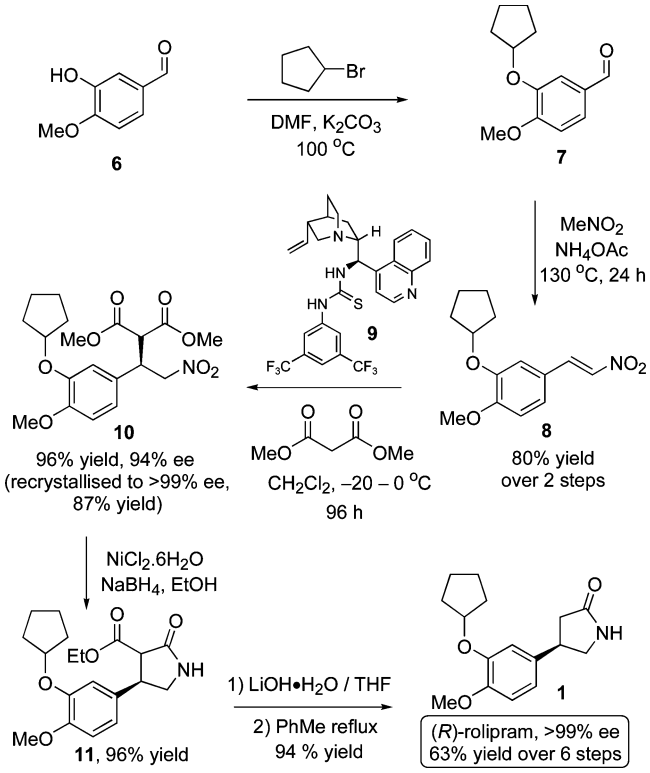
Scheme 1. Synthetic Plan to (*R*)-Rolipram **1** and (3*S*,4*R*)-Paroxetine **2** from a Michael Adduct of Malonate and Nitro Olefin



Key to the synthesis of (*R*)-rolipram **1** is the ready construction of nitro olefin **8**. This was prepared in 2 steps on multigram scale from the commercially available hydroxy aldehyde **6**. An initial alkylation using cyclopentylbromide and potassium carbonate in DMF provided ether **7** which was then subjected to standard Henry condensation conditions to give nitro olefin **8** in 80% yield over 2 steps. The enantioselective Michael addition of dimethyl malonate to **8** catalyzed by **9** occurred smoothly at −20 °C in dichloromethane; product **10** was formed in 96% yield and in 94% ee.

This material was recrystallized to enantiomeric purity from hexane/TBME, (4:1) giving an overall reaction yield of 87% to enantiopure **10**. A nickel boride reduction of the nitro group yielded the transesterified γ-lactam **11**, which was decarboxylated in a two stage hydrolysis/thermolysis procedure to afford (*R*)-rolipram **1** as a single enantiomer in 63% overall yield over six steps (Scheme 2).

Scheme 2. Total Synthesis of (*R*)-Rolipram **1**, Using Bifunctional Organocatalyst **9**



Our route to (3*S*,4*R*)-paroxetine **2** began in a similar manner. The key nitro olefin **13** was prepared in a single step from the commercially available aldehyde **12** in 92% yield. The enantioselective malonate Michael addition to **13**

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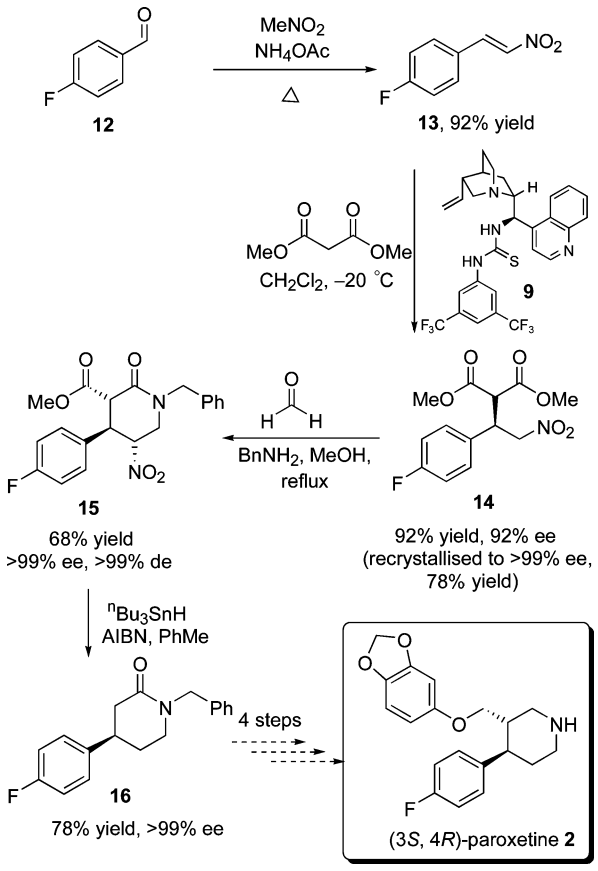
Scheme 3. Formal Synthesis of (3*S*,4*R*)-Paroxetine **2**, Using Bifunctional Organocatalyst **9**



catalyzed by **9** occurred smoothly to give the Michael adduct **14** in 92% yield and in 92% ee. Recrystallization from Et_2O/petroleum ether, (1:1) facilitated an efficient enantiomeric upgrade to greater than 99% ee in a single operation; the overall reaction yield to enantiopure **14** was 78%. With Michael adduct **14** in hand, we were then poised to investigate the one carbon homologation via the nitro-Mannich reaction. Pleasingly, treatment of **14** with benzylamine and formaldehyde in boiling methanol for 16 h lead smoothly to the δ-lactam product **14** as a single diastereoisomer in 68% yield.

For the nitro-Mannich lactamization step to be of any synthetic value in the synthesis of target paroxetine, the efficient reductive removal of the nitro group was necessary. Although Nef-type chemistry was initially considered, the reported reductive removal of nitro groups from alkanes using tributyltin hydride and AIBN was attractive and therefore investigated.[8] Pleasingly, when a modification of the Ono conditions were employed on **15** simultaneous removal of the nitro group and dealkyl decarboxylation occurred to give **16** in 78% yield. The synthesis of known compound **16** constitutes a formal total synthesis of (3*S*,4*R*)-paroxetine **2**, the route to **16** being five steps and the overall yield 38% (Scheme 3).[6d]

In summary, an efficient enantioselective total synthesis of (*R*)-rolipram **1** and an efficient enantioselective formal synthesis of (3*S*,4*R*)-paroxetine **2** has been achieved using the highly enantioselective Michael addition of malonate nucleophiles as key steps in both cases. In both routes, ready improvement to the enantiomeric excess of the Michael adduct was possible through the process of recrystallization, and therefore the effective power of bifunctional catalyst **9** in the construction of target molecules as single enantiomers has been demonstrated.

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Supporting Information Available: Experimental procedures and spectroscopic data for products **1**, **7**, **8**, **10**, **11**, **13**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org

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