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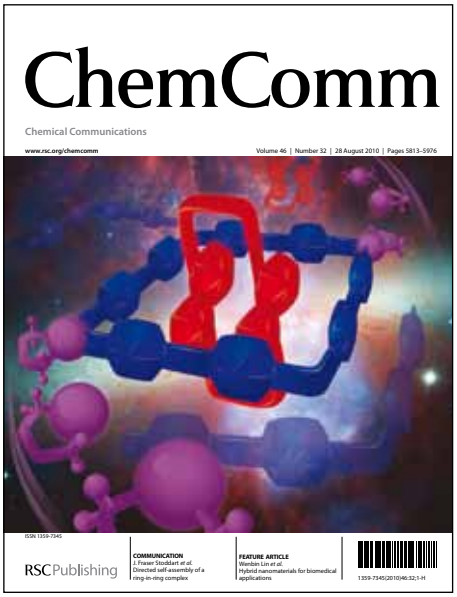

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Enantioselective Synthesis of Levomilnacipran†‡

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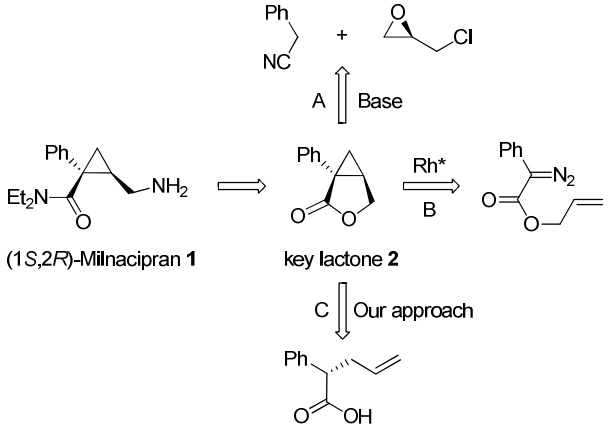
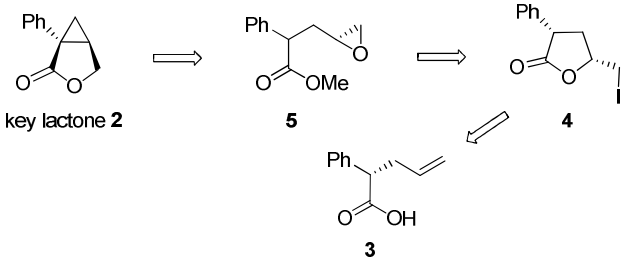
A novel approach for the asymmetric synthesis of the active (1*S*,2*R*)-enantiomer of the antidepressant milnacipran is reported. The two stereogenic centers borne by the cyclopropane ring were sequentially installed starting from phenylacetic acid.

Levomilnacipran **1** ((1*S*,2*R*)-milnacipran) is an antidepressant currently in phase III clinical trials[1] for the treatment of major depressive disorders.[2] Levomilnacipran is the most active enantiomer of milnacipran and a selective dual serotonin-norepinephrine reuptake inhibitor.[3] While several strategies have already been developed for the synthesis of milnacipran and analogous cyclopropanes in their racemic form,[4] enantioselective routes to the title compound are scarce.

Approaches that have been devised so far relied on the asymmetric construction of the key cyclopropane-fused lactone **2** where absolute configuration of the two stereogenic centers is controled (Scheme 1).[5] For example, the nucleophilic addition of phenylacetonitrile to optically active epichorohydrin under basic conditions provided efficient access to **2** through a two-step sequence (Scheme 1, Path A).[6] Also, the rhodium(II)-catalyzed asymmetric intramolecular cyclopropanation of allyl phenyldiazoacetate efficiently promoted the formation of the key intermediate **2** (Scheme 1, Path B).[7] Although the latter approach provided a concise pathway to lactone **2**, the obtained enantiomeric excesses were moderate (≤ 68% ee) regardless of the rhodium-based catalytic system. Further transformation of **2** by diethylaminolysis



Scheme 1 Enantioselective routes to milnacipran

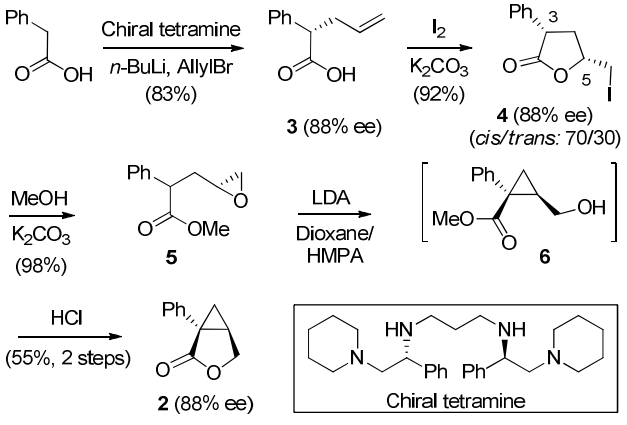


Scheme 2 Retrosynthetic approach to optically active key lactone **2**

of the lactone ring followed by interconversion of the resulting alcohol into the corresponding primary amine, finally afforded optically active milnacipran.

In this paper we report an alternative route to levomilnacipran from (2*S*)-phenylpent-4-enoic acid **3** (Scheme 1, Path C). The latter compound could be easily converted to *cis*-γ-lactone **4** by iodolactonization prior to methanolysis of the lactone ring and concomitant epoxide **5** formation *via* ring closure of the transient halohydrin (Scheme 2). Tandem cyclopropanation by S_N2 ring opening of the γ,δ-epoxide and *in situ* lactonization would then deliver the optically active target lactone **2**.

Our synthesis thus commenced with the preparation of (2*S*)-phenylpent-4-enoic acid **3** which was obtained with high enantioselectivity using the elegant methodology recently developed by Zakarian *et al.*[8] (Scheme 3). The process involved the enantioselective alkylation of phenylacetic acid using a tetramine as traceless chiral auxilary. Using the above procedure, optically active (2*S*)-phenylpent-4-enoic acid **3** was obtained in



Scheme 3 Enantioselective Approach to the Key Lactone

83% yield and 88% ee. Subsequent iodolactonisation of **3** with molecular iodine in diethyl ether afforded lactone **4**.[9] Iodoactonization selectively provided the γ-butyrolactone as the only product (92% yield) and with satisfactory diastereoselectivity since the expected *cis*-isomer was formed preferentially over the *trans*-form (*cis/trans* 70:30). The lactonization step thus proceeded with high 1,3-asymmetric induction which permitted to control the absolute configuration of the C5 position. The major *cis*-isomer **4** was recovered by column chromatography and chiral HPLC measurements indicated no erosion of the optical purity since iodolactone **4** exhibited the same enantiomeric excess (88% ee) as that of the starting phenylacetic acid derivative **3**. The lactone ring of **4** was thereafter methanolyzed in the presence of potassium carbonate. Although complete epimerization of the centre adjacent to the ester was observed under the mildly basic conditions, chiral information borne by C5 was fully retained during the ring closure step of the halohydrin intermediate into epoxide **5**. Absolute stereochemistry of the epoxide unit is a key element in our overall strategy towards the asymmetric synthesis of lactone **2** as the cyclopropanation step is expected to proceed by second order nucleophilic substitution of the epoxide with inversion of configuration. The stage was thus set for the intramolecular cyclopropanation of the γ,δ-epoxy ester **5** by S_N2 nucleophilic ring opening of the oxirane.

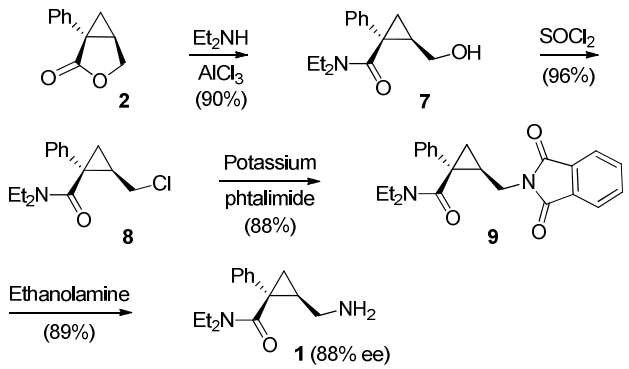
Table 1 Optimization of the Cyclopropanation Conditions

entry	solvent	temp	*cis/trans*[a]	conv (%)[a]
1	THF	rt	30:70	92
2	THF	rflx	45:55	90
3	THF/HMPA (9:1)	rflx	55:45	87
4	Dioxane/HMPA (9:1)	rflx	70:30	89

[a] Based on ^{1}H NMR analysis of the crude reaction mixture.

Attempts to run the reaction at room temperature and under various basic conditions afforded majoritarily the unwanted *trans*-cyclopropane (Table 1, Entry 1). LDA was however selected as a base and the reaction conditions were optimized to promote the preferential formation of the *cis*-isomer **6**. We found that by rising the reaction temperature to refux, the ratio of the *cis*-isomer was increased up to nearly 50% (Entry 2). The addition of HMPA also had a beneficial effect on the selective formation of **6** as the latter was now produced as the major product (Entry 3). Best results were obtained when the intramolecular nucleophilic displacement was conducted in a higher boiling point solvent such as dioxane and in the presence of HMPA. Indeed, the expected *cis*-cyclopropane **6** was obtained in good yield and with a *cis/trans* ratio of 70:30 (Entry 4). The *cis*-cyclopropane was not isolated from the crude mixture but treated *in situ* with HCl to induce clean formation of the key lactone **2** in 55% yield (over two steps) and 88% ee. Although not fully understood yet, the diastereoselectivity observed for the cyclopropanation step in the presence or in the absence of HMPA may originate from selective deprotonation of the ester. The process, which is governed by lithium coordination between the carbonyl and the epoxide, can give rise to *cis* or *trans*-enolate intermediates depending on the reaction conditions. Owing to steric interactions, each enolate evolves selectively to provide preferential access to one of the cyclopropane forms (for a model, see Figure S1 in the ESI).

At this stage, we had formally synthesized levomilnacipran considering that lactone **2**, wherein the two stereogenic centers are irreversibly set, is the classical intermediate in the known syntheses of the title compound. The preparation of levomilnacipran was nevertheless continued (Scheme 4) by diethylaminolysis of the lactone in the presence of $AlCl_3$ to afford the cyclopropyl amide-alcohol **7** in 90% yield.[10]



Scheme 4 Completion of the Synthesis of Levomilnacipran

The alcohol group was then converted into a leaving group for the ensuing introduction of the primary amine. Compound **7** was hence reacted with thionyl chloride to give halogenated derivative **8** before potassium phtalimide was added. Nuleophilic displacement of the chlorine atom by potassium phtalimide permitted efficient introduction of the amine precursor (**9**) whose deprotection with ethanolamine finally afforded levomilnacipran **1** in 89% yield.

Spectral data (^{1}H and ^{13}C NMR) of **1** are consistent with those of authentic milnacipran and optical rotation measurements gave an $[\alpha]_D$ value of −88.3 (*c* 1.0, $CHCl_3$). Noteworthy that while compound **1** is levorotatory, levomilnacipran hydrochloride is dextrorotatory ($[\alpha]_D$ +72.5 (*c* 0.7, $CHCl_3$)). However, the optical rotation sign of **1**·HCl matches that reported in the literature for (1*S*,2*R*)-milnacipran hydrochloride ($[\alpha]_D$ +72.8 (*c* 0.95, $CHCl_3$), 96% ee).[6a] Enantiomeric excess of **1** was ultimately measured by chiral HPLC which revealed a steady ee value of 88%. These results unambiguously indicate that the initial stereochemical information of the starting α-substituted phenylacetic acid **3** was fully transferred throughout our synthesis of levomilnacipran. The strategy we have developed to meet the synthetic challenge of the asymmetric synthesis of levomilnacipran may also be viewed as a general route for the preparation of optically active substituted cyclopropanes.

In summary, we reported here an efficient enantioselective synthesis of levomilnacipran from phenylacetic acid. Our approch involved the asymmetric preparation of the central lactone intermediate **2** using three key reactions: i) the enantioselective synthesis of (2*S*)-phenylpent-4-enoic acid, ii) its selective iodolactonisation, and iii) the intramolecular cyclopropanation of epoxy ester **5**. The enantiomeric excess of the starting phenylpentenoic acid **3** was preserved throughout the developed synthetic pathway, thus permitting efficient access to levomilnacipran **1** with 88% ee.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, copies of $^{1}H/^{13}C$ NMR spectra of all compounds, and a model for the selective cyclopropanation step. See DOI: 10.1039/b000000x/

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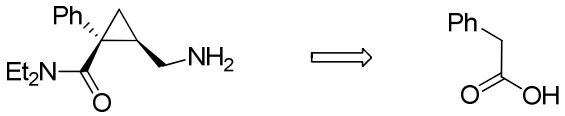
TOC Graphic



The asymmetric synthesis of Levomilnacipran is reported starting from phenylacetic acid.