ORGANIC LETTERS

2010
Vol. 12, No. 12
2826−2829

Synthesis of (−)-Paroxetine via Enantioselective Phase-Transfer Catalytic Monoalkylation of Malonamide Ester

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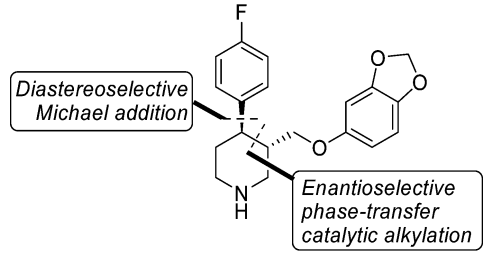
Received April 22, 2010

ABSTRACT



(-)-Paroxetine

A new enantioselective synthetic method of (−)-paroxetine is reported. (−)-Paroxetine could be obtained in 15 steps (95% ee and 9.1% overall yield) from *N,N*-bis(*p*-methoxyphenyl)malonamide *tert*-butyl ester via the enantioselective phase-transfer catalytic alkylation and the diastereoselective Michael addition as the key steps.

The piperidine ring system has been regarded as one of the most important pharmacophore units in biologically active natural products as well as in synthetic drugs.[1] Their biological activities are often quite dependent on the types and locations of their substituents and their chirality. Accordingly, enantioselective synthetic methodologies for the construction of piperidine ring systems with 3- and 4-substituents have been studied greatly thus far.[2] The usefulness of the newly developed synthetic methodologies has frequently been evaluated via their application in the enantioselective synthesis of (−)-paroxetine which possesses chiral centers at C(3) and C(4).

(−)-Paroxetine (Paxil) is a selective serotonin reuptake inhibitor that is used for the treatment of depression, anxiety, and panic disorders.[3] There have been a number of enantioselective synthetic methods for its construction. The (3*S*)- and (4*R*)-chiral centers have been introduced by resolutions,[4] chiral auxiliaries,[5] chiral bases,[6] resort to the chiral pool,[7] enantioselective catalysis,[8] and enzymatic asymmetrizations.[9] Most of them generally incorporate the (4*R*)-*p*-fluorophenyl group earlier than the (3*S*)-hydroxymethyl group, whose

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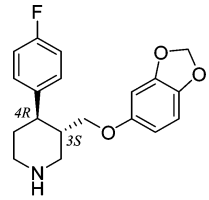
10.1021/ol100928v
Published on Web 05/25/2010

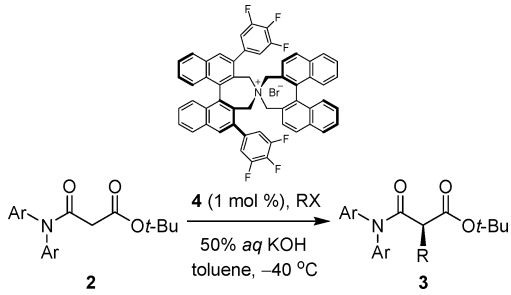
stereochemistry is often controlled by the C(4*R*) chirality. Herein, we present a novel synthetic approach to (−)-paroxetine that introduces the C(3*S*)-center first by asymmetric phase-transfer catalytic alkylation,[10] before installing the C(4)-stereocenter by diastereoselective Michael addition.



1, (–)-Paroxetine

Recently, we reported on the asymmetric catalytic "*mono*"-α-alkylation of 1,3-dicarbonyl systems (Scheme 1).[11] Malonamide esters **2** were designed as racemization-resistant malonyl substrates and were successfully applied to the enantioselective α-alkylations under phase-transfer conditions in the presence of a catalytic amount of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**4**) to afford α-monoalkylated products **3** in high chemical (up to 95%) and optical yields (up to 96% ee).

Scheme 1. Enantioselective Monoalkylation of 1,3-Dicarbonyls (Malonamide Esters)

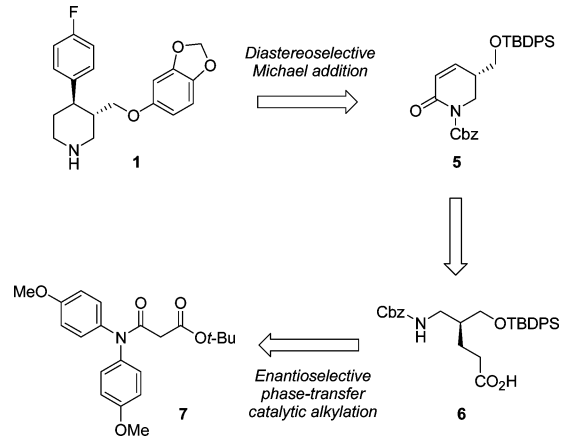


2 **3**

The low acidity of the second α-hydrogen of **3** and the $A^{1,3}$-strain between the *N*-aryl-substituents (Ar) and α-substituents (R) contributed to the resistance toward racemization of **3** during the alkylation reaction. Chiral mono-α-alkyl malonamide esters could be converted to various useful chiral synthetic intermediates, such as α-alkyl-*β*-hydroxy acids, *β*-alkyl-*γ*-amino alcohols, and α-alkyl-*β*-amino acids, by successive chemoselective reductions. Given this, we attempted to apply our method to the synthesis of one of the representative chiral 3,4-disubstituted piperidines, (−)-paroxetine (**1**).

As shown in the retrosynthetic strategy (Scheme 2), the C(4*S*) chirality can, in principle, be induced by diastereoselective conjugate addition of a *p*-fluorophenyl anionic nucleophile to chiral enone **5**, which can be obtained by lactamization and olefination of **6**. Optically active C(3*S*)-**6** can be derived from enantioselective phase-transfer catalytic alkylation of *N*,*N*-bis(*p*-methoxyphenyl) malonamide *tert*-butyl ester (**7**).

Scheme 2. Retrosynthesis of (−)-Paroxetine (**1**)



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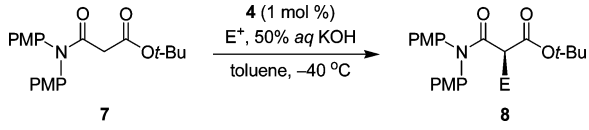
First, the phase-transfer catalytic Michael addition was carried out with **7** and methyl acrylate to introduce an α-carbomethoxyethyl moiety under the previously reported optimal reaction conditions. (*S*,*S*)-3,4,5-Trifluorophenyl-NAS bromide (**4**, 1 mol %) and 50% aqueous KOH (13.0 equiv) in toluene at −40 °C were used for this purpose (entry 1 in Table 1). However, much to our disappointment, quite low

Table 1. Enantioselective Phase-Transfer Catalytic Alkylation[a]



7 **8**

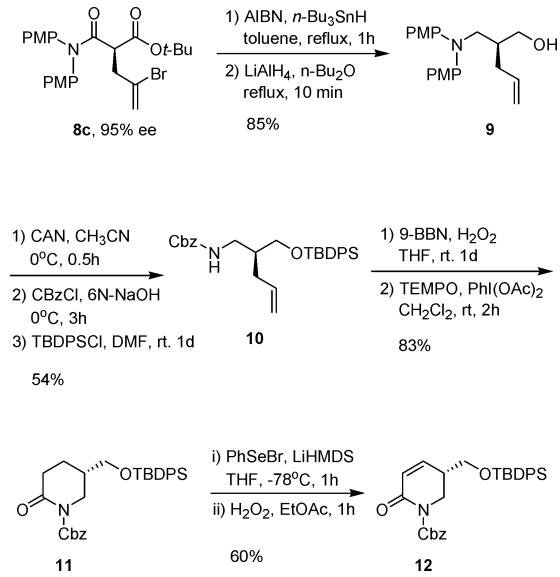
entry	electrophile (E^+)	8	time (h)	yield (%)[b]	ee (%)[c] config.[d]
1[e]		**8a**	12	60	30 (*S*)
2		**8b**	12	86	90 (*S*)
3		**8c**	12	92	95 (*S*)

[a] The reaction was carried out with 1.2 equiv of electrophile and 13.0 equiv of 50% aq KOH in the presence of catalyst **4** (1 mol %) in toluene. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis of **8** using a chiral column (Chiralcel OD) with hexane/2-propanol as an eluent; in this case, it was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] Absolute configuration was determined by comparison of the optical rotation of (−)-paroxetine (**1**) transformed from **8c** with the reported value.[5b] [e] The reaction was conducted by *s*-CsOH (1 equiv).

enantioselectivity was observed alongside low chemical yields (60%, 35% ee). Our strategy needed modification to enhance enantioselectivity, and we chose allylation as an alternate pathway which could convert to a carbomethoxyethyl moiety by further chemical transformations. The phase-transfer catalytic allylation with allyl bromide and 2-bromoallyl bromide under the same reaction conditions afforded the corresponding allylated products **8b** and **8c** with quite enhanced enantioselectivities. Notably, a higher enantioselectivity was obtained with 2-bromoallyl bromide (entry 3, 92%, 95% ee), compared to that of allyl bromide (entry 2, 86%, 90% ee). The bulkier electrophile could more selectively approach the *re*-face of the enolate of **7** when complexed with quaternary ammonium catalyst **4**, thus affording higher enantioselectivity. The absolute configuration of **8c** was determined as *S* by comparison of the optical rotation of (−)-paroxetine (**1**) {$[\alpha]_D^{22} = -75.6$ (*c* 1.00, MeOH)} obtained from **8c** with the reported values {$[\alpha]_D^{22} = -80.8$ (*c* 1.25, MeOH)}.[5b]

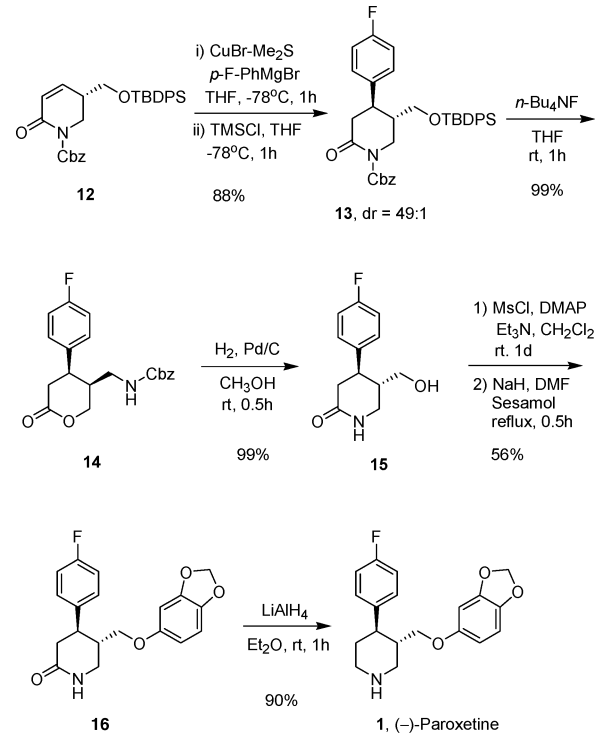
Six-membered lactam intermediate **12** was prepared from the allylated product **8c** (95% ee) in eight steps (Scheme 3). The debromination of **8c** using tributyltin hydride in the presence of a catalytic amount of AIBN in toluene, followed by reduction with $LiAlH_4$ in dibutyl ether, provided **9** (85% from **8c**). The PMP groups of **9** were removed with CAN to afford crude 3-amino-2-allylpropanol. Without purification, the amino group was protected with a Cbz group by treatment

Scheme 3. Transformation of **8c** to Chiral Michael Acceptor **12**



with benzyl chloroformate. This was followed by alcohol protection with a TBDPS group to provide **10** (54% for 3 steps). Hydroboration of **10** using 9-BBN, followed by oxidation using TEMPO/(diacetoxyiodo)benzene, directly gave the lactam **11** (83% for 2 steps). Addition of phenylselenium bromide to **11** and LiHMDS provided the corresponding α-phenylselenylated product, which was readily converted to the α,*β*-unsaturated lactam **12** with hydrogen peroxide (60% for 2 steps).

Scheme 4. Completion of the Synthesis of (−)-Paroxetine (**1**)



Next, diastereoselective Michael addition of **12** was performed to introduce the C(4*R*) chirality of **1**. The Michael addition of *p*-fluorophenyl cuprate to **12** in THF at −78 °C afforded (3*S*,4*R*)-**13** in 88% chemical yield with an excellent diastereomeric ratio of 49:1 in favor of the *trans*-lactam (Scheme 4). The *trans* relationship of the substituents at C(3) and C(4) was confirmed by the coupling constant of the protons at C(3) and C(4) in the ^{1}H NMR (500 MHz, $CDCl_3$) spectrum of **13**, showing a value of 10.5 Hz. The TBDPS group of **13** was deprotected with 0.1 M TBAF in THF (99%). Interestingly, we could only obtain the 3,4-*cis*-lactone **14** instead of the deprotected alcohol.[12] The alcohol generated by the TBDPS deprotection displaced the *N*-Cbz group of the imide **13** to give the lactone **14**. The removal of the *N*-Cbz group by catalytic hydrogenation readily furnished the lactam **15** (>99%). The etherification of **15** with sesamol was accomplished by the coupling of sodium sesamolate with the mesylate prepared from **15** by treatment with methanesulfonyl chloride (56% for 2 steps). Finally, (−)-paroxetine (**1**) was obtained by amide reduction of **16** with $LiAlH_4$ (90%).

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In conclusion, (−)-paroxetine (**1**) has been synthesized in 15 steps (9.1% overall yield, 95% ee) by enantioselective phase-transfer catalytic alkylation and diastereoselective Michael addition from *N*,*N*-bis(*p*-methoxyphenyl)malonamide *tert*-butyl ester (**7**). Further applications to the synthesis of similar compounds with a phenyl piperidine core structure having two *trans*-substituents at C(3) and C(4), such as (+)-femoxetine and Roche-1, are now under investigation.

Acknowledgment. This work was supported by the National Research Foundation (NRF) grant funded by the Korea government (MEST) (No. 201000017) and by the Midcareer Researcher Support Programs of National Research Foundation of Korea (2009-0078814).

Note Added after ASAP Publication. Scheme 4 and the SI file contained errors in the version published ASAP May 25, 2010; the correct versions reposted May 27, 2010.

Supporting Information Available: Spectroscopic characterizations of compounds **1** and **8c**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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