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Diastereoselective approach to novel octahydroisoquinolones and an extension to its one-pot synthesis

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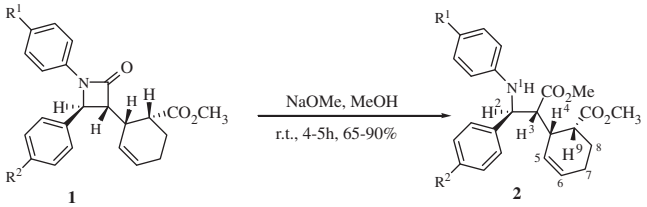
ABSTRACT

The present Letter describes the use of β-lactams for the synthesis of functionalized β-amino esters and their transformation to trisubstituted octahydroisoquinolone derivatives in good yields with an extension to their one-pot synthesis.

Isoquinolone and its derivatives constitute an important group of biologically active compounds targeted toward various therapeutic end points. These have been found to be orally effective 5-HT_3 antagonists demonstrating their high utility in cancer chemotherapy, anxiety, and schizophrenia.[1] These have also been reported to restrain the activities of thymidylate synthase involved in biological pathway of tumor growth[2] and human Tumor Necrosis Factor (TNF) for pharmacological intervention in a variety of inflammatory states such as arthritis,[3] psoriasis,[4] and cystic fibrosis.[5]

The rationalization of the literature reveals the lack of general methods for the construction of functionalized di/tetra hydroisoquinolones, and most of the existing synthetic strategies are strongly influenced by the nature of the substituents linked to the six-membered heterocyclic moiety. The major synthetic routes to 2-alkyl-3-aryl-(2*H*)-isoquinolones involve the mercury-mediated cyclization of *N*-alkylimines,[6,7] the reaction of 2′-carboxy-2-hydroxydeoxybenzoin with primary amines,[8] the treatment of homophthalic anhydride with imidoyl chlorides,[9] or the cycloaddition of benzyne to 5-phenylpyrroline-2,3-dione.[10] The oxidation of the corresponding 3,4-dihydroisoquinolones,[11] 1,2-dihydroisoquinolines, or the quaternary salts of quinoline derivatives has also been utilized for their synthesis.[12] There are also a few reports on the synthesis of substituted 2,3-dialkyl-1(2*H*)-isoquinolones derivatives.[13–15]

Although there are numerous reports concerning the synthesis of substituted-1(2*H*)-isoquinolone derivatives, there is hardly any report on the synthesis of 2,3,4-trisubstituted-1-(8*H*)-isoquinolone derivatives. As part of our continued interest in the synthesis of biologically imperative scaffolds, we have reported the utility of β-lactam synthon approach toward the synthesis of diversely functionalized pyrolloxazines.[16a] As an extension to this approach, we report herein a convenient route for the transformation of *N*-aryl-β-lactams to the biologically potent variedly functionalized novel 2,3,4-trisubstituted-1-(8*H*)-isoquinolone derivatives. The treatment of **1a–f**[16b] with sodium methoxide in dry methanol at room temperature resulted in a viscous oil which on purification through flash chromatography (hexane/EtOAc ~10:1) resulted in the isolation of 2-(1-methoxycarbonyl-2-phenyl-2-phenylamino-ethyl)-cyclohex-3-enecarboxylic acid methyl esters **2a–f** in good to excellent yields (85–90%).[17] The amino esters **2a–f** were characterized with the help of analytical data and spectral evidences (Scheme 1).[18]



1 **2**

Code	R^1	R^2	%age yield	Reaction time
2a,	Cl	H	86%	4-5h
2b	H	OCH_3	88%	4-5h
2c	H	Cl	85%	4-5h
2d	H	H	87%	4-5h
2e	Cl	OCH_3	85%	4-5h
2f	Cl	Cl	90%	4-5h

Scheme 1.

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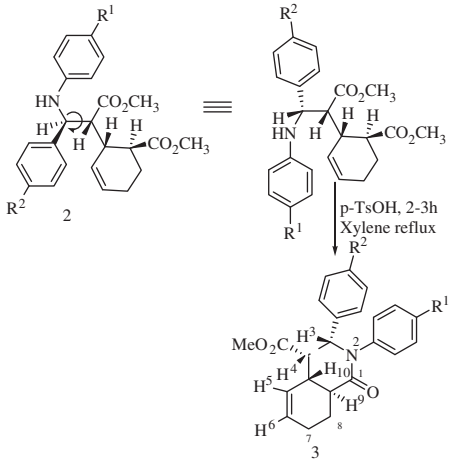
The compound **2a**, for example, analyzed for $C_{24}H_{27}NO_4Cl$ showed a molecular ion peak at *m/z* 427. Its ^{1}H NMR (300 MHz) spectrum showed a characteristic doublet at δ 4.70 (J = 3.9 Hz) assigned to H_2, a doublet of a doublet δ 2.83 (J = 3.9, 9.6 Hz) assigned to H_3, a doublet of doublet of doublet (J = 1.8, 8.1, 9.6 Hz) at δ 3.27 due to H_4, and a doublet of a triplet (J = 4.2, 6.0, 8.1 Hz) at δ 2.46 due to H_9. The presence of the requisite number of carbons in ^{13}C spectrum further corroborates the assigned structure.

The amino esters **2**, having suitably placed *N*-arylamino and carbomethoxy functionalities, are thought to be important precursors for intramolecular cyclization for the synthesis of previously unknown 2,3,4-trisubstituted-octahydroisoquinolones. The refluxing of **2** in xylene in the presence of a catalytic amount of *p*-toluene sulfonic acid resulted in the isolation of octahydro-(8*H*)-quinolone derivatives **3a–f** in good yields.[19] The formation of diastereomerically pure 2,3,4-trisubstituted-octahydroisoquinolones is a consequence of bringing closer the aforesaid latent functionalities involving C–C bond rotation in the aminoester **2** as shown in Scheme 2.

The diastereomerically pure, novel, and functionalized 2,3,4-trisubstituted-octahydro 1-isoquinolone derivatives (**3**) thus obtained were characterized with the help of analytical data and spectral evidences.[20] The compound **3d**, for example, analyzed for $C_{23}H_{23}NO_3$ showed a molecular ion peak at *m/z* 361(M^+) in its mass spectrum. Its IR spectrum showed two strong absorption peaks at 1654 cm^{-1} and 1733 cm^{-1} corresponding to the isoquinolone ring and ester carbonyls, respectively. The salient features of its ^{1}H NMR (300 MHz) spectrum include a characteristic doublet (J = 6.6 Hz) at δ 5.33 corresponding to H_3 of the isoquinolone ring, a doublet of a doublet (J = 2.7, and 6.6 Hz) at δ 3.35 corresponding to H_4 of the isoquinolone ring, and a doublet of a doublet at δ 2.58 (J = 3.0 and 12.6 Hz) assigned to H_9. The coupling constant of 12.6 Hz indicates *trans* stereochemical arrangement between H_9 and H_{10}.

The assigned structure **3** for octahydroisoquinolone was unambiguously established with the help of X-ray diffraction studies (Fig. 1).[21]

Since the above-mentioned methodology involves the amidolytic cleavage of β-lactam ring resulting in the formation of aminoesters having appropriately placed electrophilic and nucleophilic



Code	R^1	R^2	%age yield	reaction time
3a,	Cl	H	88%	2-3h
3b	H	OCH_3	87%	2-3h
3c	H	Cl	89%	2-3h
3d	H	H	92%	2-3h
3e	Cl	OCH_3	90%	2-3h
3f	Cl	Cl	85%	2-3h

Scheme 2.

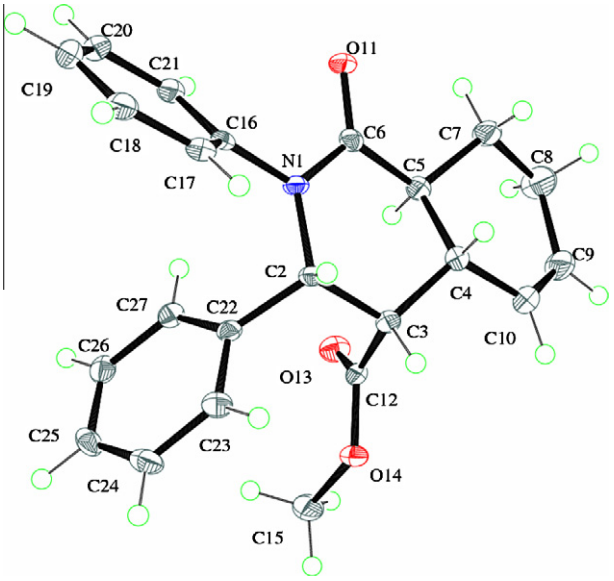
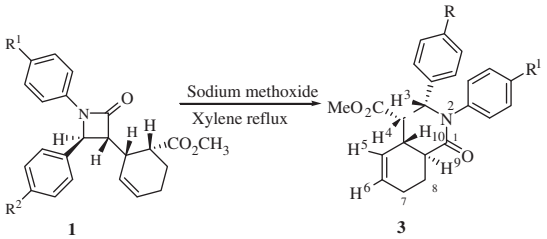


Figure 1. ORTEP diagram of **3d**.



Code	R^1	R^2	%age yield	reaction time
3a,	Cl	H	80%	4-5h
3b	H	OCH_3	82%	4-5h
3c	H	Cl	78%	4-5h
3d	H	H	86%	4-5h
3e	Cl	OCH_3	84%	4-5h
3f	Cl	Cl	85%	4-5h

Scheme 3.

groups (carbamethoxy and *N*-arylamino), it was considered worthwhile to explore the single-step transformation of β-lactam **1** to octahydroisoquinolones. For this purpose, amidolysis of **1** was attempted with sodium methoxide in refluxing xylene and this resulted interestingly in the quantitative transformation of **1**–**3** even in the absence of an acid catalyst.[22] The tlc and NMR spectra of the crude product indicated the formation of diasteromerically pure product **3**. This was further supported by the undepressed mix melting points and superimposable IR spectra with the samples of **3** obtained earlier (Scheme 3).

In conclusion, the present Letter describes an unprecedented, efficient, and highly diastereoselective synthesis of novel 1,3,4-trisubstituted-1-(8*H*)-isoquinolone derivatives using β-lactam synthon methodology. The Letter further assumes significance in being probably the first report on one-pot synthesis of novel octahydroisoquinolones. Further work on the scope and extension of this methodology are under progress and will be shortly communicated.

Acknowledgments

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References and notes

1. (a) Matsui, T.; Sugiura, T.; Nakui, H.; Iguch, S.; Shigeoka, S.; Tukedu, H.; Odagaki, T.; Ushio, Y.; Ohmoto, K.; Iwamami, M.; Yamazaki, S.; Arai, T.; Kawamura, M. *J. Med. Chem.* **1992**, *35*, 3307; (b) Briet, N.; Brookes, M. H.; Davenport, R. J.; Galvin, F. C. A.; Gilbert, P. J.; Mack, S. R.; Sabin, V. *Tetrahedron* **2002**, *58*, 5761.
2. (a) Jones, T. R.; Calvert, A. M.; Jackman, A. L.; Brown, S.; Jones, M.; Harrap, K. R. *Eur. J. Cancer* **1981**, *17*, 11; (b) Hughes, L. R.; Marsham, P. R.; Oldfield, J.; Jones, T. R.; Connor, B. M.; Bishop, J. A.; Calvert, A. H.; Jackman, A. L. *Proc. Am. Assoc. Cancer Res.* **1988**, *29*, 286.
3. Isomaki, P.; Punnonen, J. *Ann. Med.* **1997**, *29*, 499.
4. Mitzutani, H.; Ohmot, Y.; Mitzutani, T.; Murata, M.; Shimizu, M. *J. Dermatol. Sci.* **1997**, *14*, 145.
5. Bonfield, T. L.; Pansuka, J. R.; Konstan, M. W.; Hilliard, K. A.; Hilliard, J. B.; Ghnaim, H.; Berger, M. *Am. J. Respir. Crit. Care Med.* **1995**, *152*, 2111.
6. (a) Mondon, A. Erythrina Alkaloids. In *Chemistry of the Alkaloids*; Pelletier, S. W., Ed.; Van Nostrand, Reinhold: New York, 1970; p 137; (b) Whitlock, H. W., Jr.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600.
7. Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett.* **1982**, *23*, 1957; . *J. Chem. Soc., Perkin Trans. 1* **1988**, 1317.
8. Letcher, R. M.; Kwok, N.-C.; Cheung, K.-K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1769.
9. (a) Stanoeva, E.; Haimova, M. A.; Ognyanov, V. I. *Liebigs Ann. Chem.* **1984**, 389; (b) Haimova, M. A.; Ognyanov, V. I.; Mollov, N. M. *Synthesis* **1980**, 845.
10. Cobas, A.; Guitian, E.; Castedo, L. *J. Org. Chem.* **1993**, *58*, 3113.
11. Dominguez, E.; Martinez de Marigorta, E.; Carillo, L.; Fananas, R. *Tetrahedron* **1991**, *47*, 9253.
12. (a) Brooks, J. R.; Harcourt, D. N.; Waigh, R. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2588; (b) Haraoka, M.; Yamagishi, H.; Marutani, M.; Mukai, C. *Tetrahedron Lett.* **1984**, *25*, 5169.
13. Larock, R. C.; Liu, C.-L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1984**, *25*, 4459.
14. Singh, R.; Singh, R. P.; Srivastava, J. N. *J. Indian Chem. Soc.* **1991**, *68*, 276.
15. (a) Couture, A.; Grandclaudon, P.; Hooijer, S. *J. Org. Chem.* **1991**, *56*, 4977; (b) Couture, A.; Grandclaudon, P. *Synthesis* **1986**, 576.
16. (a) Anand, A.; Bhargava, G.; Kumar, V.; Mahajan, M. P. *Tetrahedron Lett.* **2010**, *51*, 2312; (b) Bhargava, G.; Anand, A.; Mahajan, M. P.; Saito, T.; Sakai, K.; Chitrani, M. *Tetrahedron* **2008**, *64*, 6801.
17. *General procedure for the N1–C2 bond cleavage of 2-(2-oxo-1,4-diaryl-azetidin-3-yl)-cyclohex-3-enecarboxylic acid methyl ester* **2**: A solution of sodium methoxide (2 mmol) in dry methanol was added dropwise to a stirred solution of **1** (2 mmol) in dry methanol. The progress of the reaction was monitored through tlc and on completion, was quenched with water (50 mL) and the reaction mixture was extracted with dichloromethane (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuo. The crude product thus obtained was purified by flash chromatography on silica gel using a mixture (10:1) of hexane and ethyl acetate as an eluent.
18. *2-[2-(4-Chloro-phenylamino)-1-methoxycarbonyl-2-phenyl-ethyl]-cyclohex-3-enecarboxylic acid methyl ester* (**2a**): viscous liquid, δ_H ($CDCl_3$, 300 MHz), 1.90 (m, 2H, H_7), 2.05 (m, 2H, H_8), 2.46 (dt, J = 4.2, 6.0, 8.1 Hz, 1H, H_9), 2.83 (dd, J = 3.9, 9.6 Hz, 1H, H_3), 3.27 (ddd, J = 1.8, 8.1, 9.6 Hz, 1H, H_4), 3.42 (s, 3H, $-OCH_3$), 3.60 (s, 3H, $-OCH_3$), 4.70 (d, J = 3.9 Hz, 1H, H_2), 5.70 (dt, J = 1.5, 3.9, 8.1 Hz, 1H, H_6), 5.81 (dd, J = 1.8, 8.1 Hz, 1H, H_5), 6.43 (dd, J = 8.1 Hz, 2H, aromatic), 6.98 (dd, J = 8.1 Hz, 2H, aromatic), 7.23 (m, 5H, ArH) δ_C ($CDCl_3$,75 MHz), 22.8, 35.4, 42.1, 45.3, 55.2, 55.4, 61.2, 64.3, 116.3, 122.5, 125.4, 127.8, 128.2, 128.5, 129.1, 129.5, 129.7, 137.4, 171.5, 173.8, m/z 427 $(M)^+$. ν_{max} (KBr)/cm^{-1} 1731, 1729, 1650, 1602, 1508, 1434, 1365, 1315. Anal. Calcd for $C_{24}H_{26}NO_4Cl$: C, 67.36; H, 6.12; N, 3.27. Found: C, 67.50; H, 6.01; N, 3.32.
19. *Procedure for the synthesis of octahydroisoquinolone derivatives from the corresponding esters* **3a–f**: The typical procedure for the formation of octahydroisoquinolone derivatives **3a–f** involved the refluxing of amino esters **2a–f** in xylene containing catalytic amount of *p*-toluene sulfonic acid. The progress of reaction was monitored with the help of tlc. The crude product obtained after removal of solvent under reduced pressure was subjected to column chromatography on silica gel (eluent: a mixture of EtOAc/hexane in a 2:3 ratio) to yield octahydroisoquinolone derivatives **3**. The products were recrystallized with a mixture of ethylacetate/hexane (1:4).
20. *1-Oxo-2,3-diphenyl-1,2,3,4,4a,7,8,8a-octahydro-isoquinoline-4-carboxylic acid methyl ester* (**3d**) White solid, mp 147–148 °C δ_H ($CDCl_3$, 300 MHz), 1.42 (m, 2H, $H_{8a,\ 8b}$), 2.23 (m, 2H, $H_{7a,\ 7b}$), 2.58 (dd, J = 3.0, 12.6 Hz, 1H, H_9), 3.26 (s, 3H, $-OCH_3$), 3.35 (dd, J = 2.7, 6.6 Hz, 1H, H_4), 3.39 (ddd, J = 1.8, 2.7 and 12.6 Hz, 1H, H_{10}), 5.33 (d, J = 6.6 Hz, 1H, H_3), 5.53 (dd, J = 1.8, 9.9 Hz, 1H, H_5), 5.81 (ddd, J = 3.3, 6.3, and 9.9 Hz, 1H, H_6), 7.18 (m, 10H, H, aromatic), δ_C ($CDCl_3$, 75 MHz), 23.1, 25.8, 37.7, 38.5, 50.8, 51.2, 65.1, 126.2, 127.3, 127.5, 127.8, 127.9, 129.1, 130.8, 135.8, 137.5, 138.4, 170.7, 173.4, m/z 361(M^+).ν_{max} (KBr)/cm^{-1} 1733, 1654, 1490. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.57; H, 6.50; N, 3.76.
21. *X-ray crystal data and structure refinement for* **3d**: CCDC 769732 (for **3d**) contains the supplementary data for this Letter. $C_{23}H_{23}NO_3$, V = 1837.10(10) $Å^3$, Mr = 361.42, Z = 4, orthorhombic, $P2_12_12_1$, MoK_α a = 9.4319(3) Å, b = 9.6945(3), c = 20.0913(6), μ = 0.086 mm^{-1}, T = 100 (2) K 0.28 × 0.24 × 0.04 mm, data collection: BrukerAXS ApexII-CCD area detector diffractometer, absorption correction: multi-scan BRUKER SADABS, T_{min} = 0.9966, T_{max} = 0.9763, final R indices [$I > 2\sigma(I)$], R_1 = 0.0394, wR_2 = 0.0829, R indices (all data), R_1 = 0.0529, wR_2 = 0.0876, for all data, total reflections collected/unique = 3749/3749 [R(int) = 0.00], GOF = 1.032.
22. *Procedure for one-pot synthesis of octahydroisoquinolone derivatives* **3a–f**: The typical procedure for one-pot synthesis involved the refluxing of **1** (1 mmol) with sodium methoxide (2.5 mmol) in xylene for about 4–5 h. The progress of reaction was monitored with the help of tlc and the crude product after removal of solvent under reduced pressure was purified through column chromatography using a mixture (2:3) EtOAc/hexane. The products were recrystallized with a mixture of ethylacetate/hexane (1:4).