

SYNTHETIC ANALOGUES OF ALKALOID CHERYLLINE

Stanimir Manolov, Iliyan Ivanov, Stoyanka Nikolova

University of Plovdiv, Department of Organic Chemistry, 24 Tzar Assen str., 4000 Plovdiv, Bulgaria

Abstract

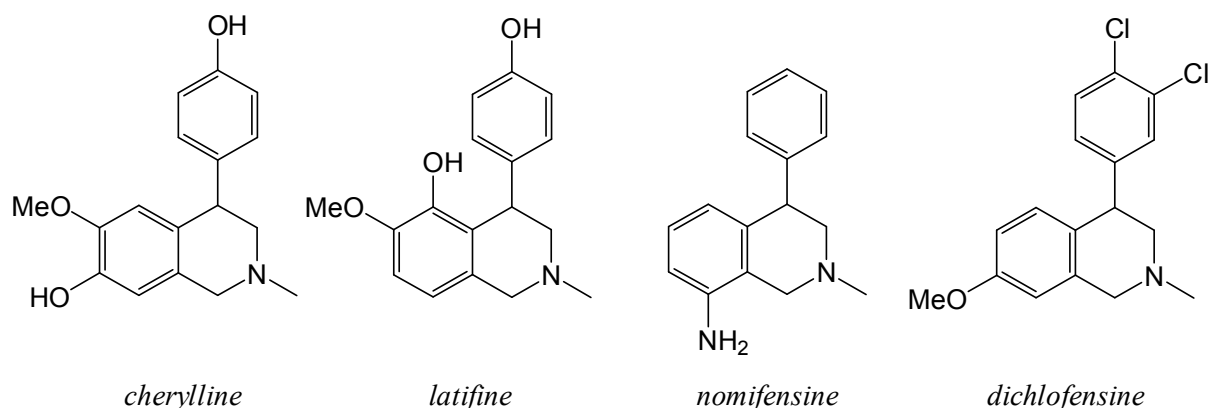
An application of α -amidoalkylation reaction, as an alternative efficient synthesis of analogues of cherylline, is reported. The required for this purpose amides would arise from reaction of aminoacetaldehyd-dimethylacetal with veratrole (1,2-dimethoxybenzene) in polyphosphoric acid, followed by acylation of obtained amines with different acid chlorides or sulfochlorides. Variety of reaction conditions – acidity of milieu, temperature and reaction time, were used for optimization the conditions for the final cyclization stage.

Key words: cherylline, 4-aryl- tetrahydroisoquinolines, α -amidoalkylation reaction

1. INTRODUCTION

Many tetrahydroisoquinoline alkaloids show interesting biological activities. One of them are Amaryllidaceae^{1,2} family which has been one of the most studied because of its alkaloids composition. In 1970, Brossi et al.³ isolated an alkaloid with 4-aryl-1,2,3,4-tetrahydroisoquinoline structure named cherylline from *Crinum Powellii*.

It is a representative of the very rare natural 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloids. Some of them are valuable medicines with centrally stimulating, thymoleptic, and antiarrhythmic actions.^{4,5} Others exhibit broad spectrum calcium antagonistic,⁶ antibacterial,⁷ antiplasmodial,^{2,8-11} estrogen agonist/antagonist activity,¹² and serotonin (5-HT) re-uptake.¹³



Due to the uniqueness of the structure and potential medicinal properties of the 4-arylisquinoline derivatives,¹⁴ many synthetic routes for these compounds¹⁵ and especially cherylline have been reported. Hence, the formation of the nitrogen-containing ring of 4-aryl-1,2,3,4-tetrahydroisoquinolines has been achieved with several reactions such as Bischler-Napieralski,¹⁶⁻¹⁸ intramolecular Horner,¹⁹ Friedel-Crafts,^{11,19-25} followed by reduction, reductive amination-transfer hydrogenation²⁶, electrophilic aromatic substitution²⁷, Pd(II)- or Ag(I)-catalyzed N-alkylation²⁸, and

palladium-catalyzed alkylation/alkenylation-aza-Michael addition reactions²⁶; Pictet-Spengler,²⁹ and oxazoline driven chemistry³⁰ among others.^{17, 31-38}

2. RESULTS AND DISCUSSION

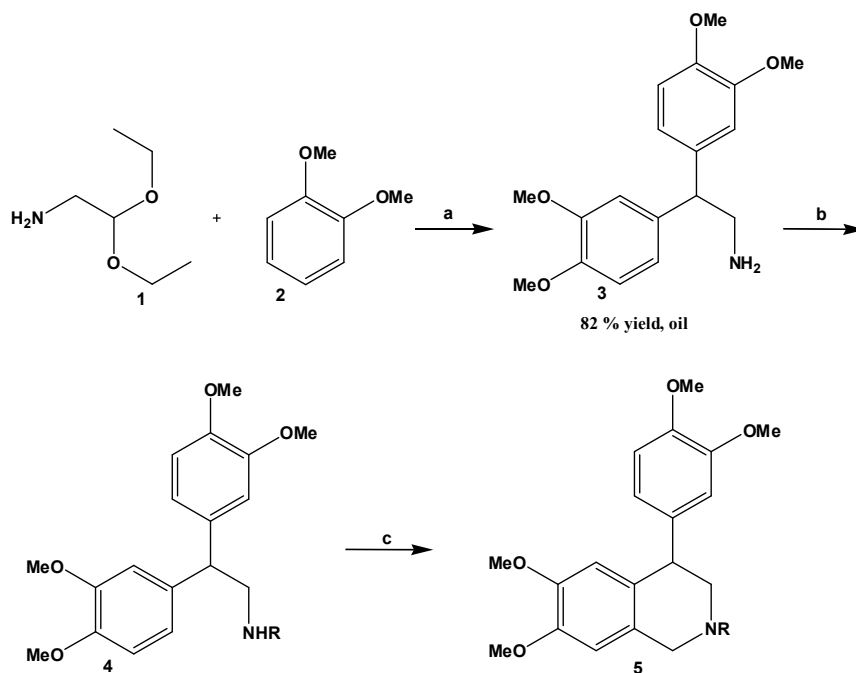
Due to the uniqueness of its structure and owing to the potential medicinal properties of the 4-arylisoquinoline derivatives, many investigations have been carried out on this class of alkaloids. There are several reports for the syntheses of cherylline. However, these methods require multistep sequences and are not focused on achieving synthetic efficiency by application of the contemporary methods involving the generation of several bonds in a single operation³⁹.

Cherylline has been prepared from the trihydroxy derivatives by adapting a sophisticated route which mimics the biogenetic pathway operative in the formation of *Amarylidaceae*⁴⁰. It is also accessible by a synthetic route based upon the Bischler-Napieralski reaction of N-formyl⁴¹ and isocyanide⁴² derivatives of polyalkoxyphenethylamines accompanied by several protection and deprotection steps. This synthetic approach has also been successfully used for the enantioselective synthesis of (–)-cherylline which could equally be obtained by Polonovski reaction of correctly substituted dibenzozacine N-oxides⁴³. Thus cherylline has been synthesized in different ways, the most common ones involving the acid-catalyzed cyclization of suitably substituted norbelladine derivatives^{19,40,41,44}. The methods employed differ mainly in the nature of the leaving group (OR, OH or X) prone to generate the carbocationic species involved in the annulation step. Cresente-Campo et al.⁴⁵ present simple and efficient method for the synthesis of 4-aryl-1,2,3,4-tetrahydroisoquinoline alkaloids from acetophenones following a linear sequence of three chemical operations, which include hydroamination of an enol carbamate as a key step. Kale et al. reported an alternative synthesis of (±)-cherylline dimethyl ether, the key step of which involved Michael addition, radical azidonation of aldehydes⁴⁶, Curtius rearrangement, and reduction of an isocyanate intermediate followed by Pictet-Spengler cyclization⁴⁷. An alternative synthesis of (±)-cherylline dimethyl ether also was reported⁴⁸. The steps involved were acid-catalyzed Michael addition of veratrole to p-methoxycinnamic acid, Curtius rearrangement, reduction of isocyanate intermediate followed by Pictet-Spengler cyclization. Ruchirawat et al.¹⁷ described another route for the synthesis of 4-aryltetrahydroisoquinolines, especially cherylline, using the addition of Grignard reagents to nitrostyrene derivatives as the key step. Kametani³⁵ reported synthesis of cherylline from starting addition of 1-equivalent of bromine to 4-benzyloxystyrene to 4-benzyloxy- α,β -dibromoethylbenzene, which was converted to 4-benzyloxy- β -methoxyphenethyl bromide. Fusion of this compound with 3-benzyloxy-4-methoxy-N-benzylamine gave the tertiary amine whose cyclization followed by debenzylation afforded (±)-cherylline. Lebrun³⁸ devised new method for the preparation of enantiopure (+) and (–)-cherylline through reduction of a diarylenamine equipped with a chiral auxiliary, concomitant and differentiated deprotections followed by ultimate cyclization.

Recently, Balamurugan³⁹ described a facile and convergent one-pot three-component protocol for the synthesis of polysubstituted tetrahydroisoquinolines of potential pharmaceutical and biological importance, via a domino Knoevenagel condensation/Michael addition/Thorpe-Ziegler cyclization/air-promoted dehydrogenation sequence.

Kumar⁴⁹ described synthesis of cherylline from starting nitrostyrenes and veratrole or anisole in trifluoroacetic acid. Subsequent reduction of nitro group, followed by Pictet-Spengler reaction gave corresponding products.

There are number of synthetic routes for the synthesis of cherylline and its derivatives but there are have no data about application of α -amidoalkylation reaction for its synthesis. In continuation of our work in developing efficient methods for the synthesis of alkaloids, we report herein application of α -amidoalkylation reaction, an alternative efficient synthesis of cherylline derivatives.



Scheme 2. (a) PPA, rt; (b) CH_3COCl or $\text{CH}_3\text{SO}_2\text{Cl}$, NEt_3 , rt;
(c) CH_2O , $\text{CH}_3\text{COOH}:\text{CF}_3\text{CCOOH} = 4:1$ rt

We tried to applied Klumpp's⁵⁰ protocol for the synthesis of required starting materials, between amino acetals and veratrole in the presence of polyphosphoric acid instead of triflic acid. We have found that aminoacetaldehyd-dimethylacetal react with excess of 1,2-dimethoxybenzene (veratrol) in PPA at rt to give good (91%) yield of corresponding product **3** (Scheme 2). We obtained the amine **3** with 89-91% yields.

The required for the next step of our synthesis amides **4** we prepared by acylation of obtained amines **3** with acetyl chloride and methanesulfonyl chloride.

Table 1

4	R	Yield, %	mp, °C	5	R	Yield, %	mp, °C
a	COCH_3	91	126-128	a	COCH_3	89	oil
b	SO_2CH_3	90	49-52	b	SO_2CH_3	87	155-159

The next step was the cyclization of the newly synthesized hydroxyamides. We applied the α -amidoalkylation reaction for the synthesis of cherylline derivatives. Variety of reaction conditions – acidity of milieu, temperature and reaction time, were used for optimization the conditions for the final cyclization stage. The obtained results show that 4-aryl-N-acyl-1,2,3,4-tetrahydroisoquinolines **5** have been obtained with good yields in the milieu of acetic:trifluoroacetic acid=4:1 for 8h at room temperature (for sulfonamides) or by heating for the others - 80°C, 3h.

Finally, we succeeded to prepare cherylline derivatives using simple protocol. For the final cyclization step we applied the α -amidoalkylation reaction as an alternative efficient method for the synthesis of cherylline analogues.

3. EXPERIMENTAL SECTION

Reagents and chemicals were purchased from commercial sources [Fluka and Merck] and used as received. Melting points were determined on a Boetius hostage apparatus and are uncorrected. Spectra were recorded on a Bruker Avance DRX250 spectrometer. ^1H -NMR and ^{13}C -NMR spectra were taken in CDCl_3 at 250 MHz and 62.5 MHz respectively. Chemical shifts were given in part per million (ppm) relative and were referenced to TMS ($\delta=0.00\text{ppm}$) as an internal standard and coupling constants are indicated in Hz. All the NMR spectra were taken at rt (ac. 295 K). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates. Merck silica gel 60 (0.063-0.2mm) was used for column chromatographic separation. Polyphosphoric acid was obtained from 85% phosphoric acid and P_2O_5 (1:1 w/w).

Synthesis of 2,2-bis(3,4-dimethoxyphenyl)ethanamine 3.

Aminoacetaldehyde dimethylacetal **1** (0.37 g, 2 mmol) was dissolved in 22.47 mmol of the veratrole in an open flask and polyphosphoric acid (5 g) was added. The reaction mixture was stirred for 20 min at rt. After completion of the reaction, the mixture was poured over ice. The organic layer was removed and after that the water layer the solution was carefully alkalized with 25 % ammonia, then extracted with CH_2Cl_2 (3x20 mL). Combined extracts were dried (Na_2SO_4) and concentrated. The products, after evaporation of the solvent, were purified by column chromatography on silica gel using Et_2O as eluent.

^1H -NMR: 1.77 (broad s, 2H, NH_2), 3.24 (dd, 2H, $J=4.6, 7.9$, CH_2), 3.78 (s, 6H, $2\times\text{OCH}_3$), 3.87 (td, 1H, $J=7.1, 10.3$, CH), 6.85 (ddd, 4H, $J=2.3, 4.9, 6.6$, Ar), 7.12-7.21 (m, 4H, Ar); ^{13}C -NMR: 135.2, 134.7, 132.2, 131.5, 129.3, 128.9, 127.6, 127.4, 120.6, 114.1, 113.9, 110.9, 55.5, 55.3, 53.4, 46.3.

Acylation of amines 3 – typical procedure for amides 4.

To the solution of 1 mmol of amine **3** in dichloromethane equal amount of acetyl chloride or methanesulfonyl chloride was added. After 10 min a little excess of triethylamine was added. After 30 min the solution was washed with diluted hydrochloric acid, saturated solution of Na_2CO_3 and water. The organic layer was dried (Na_2SO_4), concentrated and filtered on short column with neutral Al_2O_3 .

N-(2,2-bis(3,4-dimethoxyphenyl)ethyl)acetamide 4a, ^1H -NMR: 1.91 (s, 3H, CH_3), 3.82-3.90 (m, 2H, CH_2), overlapped with 3.85 (s, 6H, $2\times\text{OCH}_3$), 3.87 (s, 6H, $2\times\text{OCH}_3$), 4.08 (t, 1H, $J=7.9$, CH), 5.46 (t, 1H, $J=5.7$, NH), 6.76 (dd, $J=1.9, 5.8$, 2H, Ar), 6.81 (d, $J=1.9$, 2H, Ar), 6.83 (s, 1H, Ar), 6.86 (s, 1H, Ar); ^{13}C -NMR: 170.0, 149.1, 147.9, 134.5, 119.7, 111.5, 111.3, 55.89, 55.86, 49.7, 44.0, 23.3.

N-(2,2-bis(3,4-dimethoxyphenyl)ethyl)methanesulfonamide 4b, ^1H -NMR: 2.84 (s, 3H, CH_3), 3.67 (d, 2H, $J=7.7$, CH_2), 3.83 (s, 6H, $2\times\text{OCH}_3$), 3.85 (s, 6H, $2\times\text{OCH}_3$), 4.09 (t, 1H, $J=7.8$, CH), 4.32 (broad s, 1H, NH), 6.74 (dd, 2H, $J=1.8, 9.8$, Ar), 6.80 (d, 2H, $J=1.9$, Ar), 6.81 (s, 1H, Ar), 6.84 (s, 1H, Ar); ^{13}C -NMR: 149.3, 148.2, 133.6, 119.7, 111.5, 111.4, 55.94, 55.91, 50.4, 47.7, 40.5.

Cyclization of amides 4 with paraformaldehyde – typical procesure.

Amides **4** (3 mmol) and a little excess of paraformaldehyde were dissolved in a mixture of $\text{CH}_3\text{COOH}/\text{CF}_3\text{COOH}=4:1$ and the solution was refluxed for 2 h. The mixture was poured on the water and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers was washed with 20 % aq. Na_2CO_3 and water, dried with Na_2SO_4 . The solvent was disstiled and the products were purified by column chromatography on neutral Al_2O_3 .

1-(4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1H)-yl)ethanone 5a, ^1H -NMR: 1.66 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 3.81 (s, 6H, $2\times\text{OCH}_3$), 3.90 (s, 6H, $2\times\text{OCH}_3$), 4.90 (t, 1H, $J=1.0$, CH), 5.37 (d, 2H, $J=5.9$, CH_2), 6.47 (s, 1H, Ar), 6.59 (dd, 1H, $J=1.96$, 3.8, Ar), 6.69 (s, 1H, Ar), 6.74-6.82 (m, 2H, Ar); ^{13}C -NMR: 170.0, 149.0, 148.3, 148.1, 148.0, 135.5, 127.9, 125.1, 120.7, 111.8, 111.4, 111.2, 109.2, 108.6, 56.2, 56.0, 55.93, 55.89, 51.5, 44.6, 43.9, 20.9.

4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline 5b, ^1H -NMR: 2.72 (s, 3H, CH_3), 3.41 (dd, 1H, $J=7.4$, 12.4, CH_2), 3.72 (s, 3H, OCH_3), 3.84 (dd, 1H, $J=3.1$, 9.8, CH_2), overlapped with 3.84 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.21 (dd, 1H, $J=5.6$, 6.2, CH), 4.49 (s, 1H, CH_2), 4.52 (s, 1H, CH_2), 6.46 (s, 1H, Ar), 6.64 (s, 1H, Ar), 6.67-6.71 (m, 2H, Ar), 6.81-6.85 (m, 1H, Ar); ^{13}C -NMR: 149.0, 148.2, 148.1, 135.0, 128.2, 124.1, 121.0, 112.1, 111.9, 111.2, 108.5, 56.0, 55.9, 51.1, 47.3, 44.3, 36.3.

ACKNOWLEDGEMENTS:

We acknowledge financial support from the National Fund for scientific research DO-02-195 and Fund for scientific research of the Plovdiv University.

REFERENCES

1. Shamma, M.; Moniot, J. L In Isoquinoline Alkaloids Research: 1973-1977; Plenum: New York, NY, 1978; p 389
2. Labrana, J.; Machocho, A. K.; Kricsfalussy, V.; Brun, R.; Codina, C.; Viladomat, F.; Bastida, J. *Phytochemistry* 2002, 60, 847.
3. Brossi, A.; Grethe, G.; Tietel, S.; Wildman, W. C.; Bailey, D. T. *J. Org. Chem.* 1970, 35, 1100.
4. Jacob, J. N.; Nichols, D. E.; Kohli, J. D.; Glock, D. *J. Med. Chem.* 1981, 24, 1013.
5. Elgorashi, E. E.; Stafford, G. J.; Jager, A. K.; Van Staden, J. *Planta Med.* 2006, 72, 470.
6. Dong, H.; Sheng, J.Z.; Lee, C. M.; Wong, T. M. *Br. J. Pharmacol.* 1993, 109, 113.
7. Bernan, V. S.; Montenegro, D. A.; Korshalla, J. D.; Maiese, W. M.; Steinberg, D. A.; Greenstein, M. *J. Antibiot.* 1994, 47, 1417.
8. Ratsimamanga-Urverg, S.; Rasoanaivo, P.; Rafatro, H.; Robijaona, B.; Rakoto-Ratsimamanga, A. *Ann. Trop. Med. Parasitol.* 1994, 88, 271.
9. Maryanoff, B. E.; Vaught, J. L.; Shank, R. P.; McComsey, D. F.; Costanzo, M. J.; Nortey, S. O. *J. Med. Chem.* 1990, 33, 2793.
10. Zara-Kaczian, E.; Gyorgy, L.; Deak, G.; Seregi, A.; Doda, M. *J. Med. Chem.* 1986, 29, 1189.
11. Riggs, R. M.; Nichols, D. E.; Foreman, M. M.; Truex, L. L. *J. Med. Chem.* 1987, 30, 1887.
12. Chesworth, R.; Zawistoski, M. P.; Lefker, B. A.; Cameron, K. O.; Day, R. F.; Mangano, F. M.; Rosati, R. L.; Colella, S.; Petersen, D. N.; Brault, A.; Lu, B.; Pan, L. C.; Perry, P.; Ng, O.; Castleberry, T. A.; Owen, T. A.; Thompson, D. D.; DaSilva-Jardine, P. *Bioorg. Med. Chem. Lett.* 2004, 14, 2729.
13. Keith, J. M.; Barbier, A. J.; Wilson, S. J.; Miller, K.; Boggs, J. D.; Fraser, I. C.; Mazur, C.; Lovenberg, T. W.; Carruthers, N. I.; *Bioorg. Med. Chem. Lett.* 2007, 17, 5325.
14. (a) Jacob, J. N.; Nichols, D. E.; Kohli, J. D.; Glock, D. *J. Med. Chem.* 1981, 24, 1013. (b) Zara-Kaczian, E.; Gyorgy, L.; Deak, G.; Seregi, A.; Doda, M. *J. Med. Chem.* 1986, 29, 1189. (c)

- Maryanoff, B. E.; Vaught, J. L.; Shank, R. P.; McComsey, D. F.; Costanzo, M. J.; Nortey, S. O. *J. Med. Chem.* 1990, 33, 2793. (d) Kihara, M.; Ikeuchi, M.; Yamauchi, A.; Nukatsuka, M.; Matsumoto, H.; Toko, T. *Chem. Pharm. Bull.* 1997, 45, 939.
15. (a) Venkov, A. P.; Vodenicharov, D. *Synthesis* 1990, 253-255. (b) Kihara, M.; Kashimoto, M.; Kobayashi, Y.; Kobayashi, S. *Tetrahedron Lett.* 1990, 31, 5347. (c) Venkov, A. P.; Vodenicharov, D. M.; Ivanov, I. I. *Synthesis* 1991, 476. (d) Kihara, M.; Kashimoto, M.; Kobayashi, Y.; Nagao, Y. *Heterocycles* 1992, 34, 747. (e) Coskun, N.; Sümengen, D. *Synth. Commun.* 1993, 23, 1393. (f) Miller, R. B.; Svoboda, J. J. *Synth. Commun.* 1994, 24, 1187. (g) Meda, N.; Selvakumar, N.; Kraus, G. A. *Tetrahedron* 1999, 55, 943. (h) Kuster, G. J.; Kalmoua, F.; Gelder, de R.; Scheeren, H. W. *Chem. Commun.* 1999, 855. (i) Nolellino, L.; D'Ischia, M.; Prota, G. *Synthesis* 1999, 793. (j) Kihara, M.; Andoh, J. I.; Yoshida, C. *Heterocycles* 2000, 53, 359.
16. Brossi, A.; Teitel, S. *Tetrahedron Lett.* 1970, 11, 417.
17. Ruchirawat, S.; Tontoolarug, S.; Sahakitpichan, P. *Heterocycles* 2001, 55, 635.
18. Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* 1985, 2447.
19. Couture, A.; Deniau, E.; Lebrun, S.; Grandclaoudon, P. *J. Chem. Soc., Perkin Trans. 1* 1999, 789.
20. Cuevas, J. C.; Snickus, V. *Tetrahedron Lett.* 1989, 30, 5837.
21. Philippe, N.; Denivet, F.; Vasse, J.-L.; Sopkova-de Olivera Santos, J.; Levacher, V.; Dupas, G. *Tetrahedron* 2003, 59, 8049.
22. Hara, H.; Shirai, R.; Hoshino, O.; Umezawa, B. *Heterocycles* 1983, 20, 1945.
23. Venkov, A. P.; Vodenicharov, D. *Synthesis* 1990, 253.
24. Toda, J.; Sonobe, A.; Ichikawa, T.; Saitoh, T.; Horiguchi, Y.; Sano, T. *ARKIVOC* 2000 (ii) 165.
25. Hara, H.; Shirai, R.; Hoshino, O.; Umezawa, B. *Chem. Pharm. Bull.* 1985, 33, 3107.
26. Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* 2003, 5, 4227.
27. Fuchs, J. R.; Funk, R. L. *Org. Lett.* 2001, 3, 3349.
28. Eustache, J.; Van de Weghe, P.; Nouen, D. L.; Uyehara, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem.* 2005, 70, 4043-4053.
29. Couture, A.; Deniau, E.; Grandclaoudon, P.; Lebrun, S. *Tetrahedron Asymmetry* 2003, 14, 1309.
30. Seijas, J. A.; Vázquez-Tato, M. P.; Martínez, M. M.; Pizzolatti, M. G. *Tetrahedron Lett.* 2005, 46, 5827.
31. Irie, H.; Shiina, A.; Fushimi, T.; Katakawa, J.; Fujii, N.; Yajima, H. *Chem. Lett.* 1980, 875.
32. Katakawa, J.; Yoshimatsu, H.; Yoshida, M.; Zhang, Y.; Irie, H.; Yajima, H. *Chem. Pharm. Bull.* 1988, 36, 3928.
33. Kessar, V.; Singh, P.; Chawla, R.; Kumar, P. *J. Chem. Soc., Chem. Commun.* 1981, 1074.
34. Schwartz, M. A.; Scott, S. W. *J. Org. Chem.* 1971, 36, 1827.
35. Kametani, T.; Takahashi, K.; Van Loc, C. *Tetrahedron* 1975, 31, 235.
36. Honda, T.; Namiki, H.; Saton, F. *Org. Lett.* 2001, 3, 631.
37. Freter, K.; Dubois, E.; Thomas, A. *J. Heterocycl. Chem.* 1970, 7, 159.
38. Lebrun, S.; Couture, A.; Deniau, E.; Grandclaoudon, P. *Org. Biomol. Chem.* 2003, 1, 1700.

39. Balamurugan, K.; Jeyachandran, V.; Perumal, S.; Menendez, J. C. *Tetrahedron* 2011, 67, 1432.
40. (a) Couture, A.; Deniau, E.; Grandckaudon, P. *Tetrahedron Lett.* 1995, 36, 2483. (b) Bakker, B. H.; Tjin A-Lim, D. S.; Van der Gen, A. *Tetrahedron. Lett.* 1984, 25, 4259.
41. Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. *Tetrahedron* 1993, 49, 1431.
42. Couture, A.; Deniau, E.; Grandckaudon, P. *Tetrahedron Lett.* 1993, 34, 1479.
43. (a) Couture, A.; Deniau, E.; Gimbert, Y.; Grandckaudon, P. *J. Chem. Soc., Perkin Trans. 1* 1993, 2463. (b) Couture, A.; Deniau, E.; Grandckaudon, P.; Woisel, P. *Tetrahedron*, 1996, 52, 4433. (c) Nomoto, T.; Nasui, N.; Takayama, H. *J. Chem. Soc., Chem. Commun.* 1984, 1646.
44. Couture, A.; Deniau, E.; Woisel, P.; Grandckaudon, P.; Carpentier, J. F. *Tetrahedron Lett.* 1996, 37, 3697.
45. Cresente-Campo, J.; Vazquez-tato, M. P.; Seijas, J. A. *Tetrahedron* 2009, 65, 2655.
46. Marinescu, L.; Thinggaard, J.; Thomsen, I. B.; Bols, M. *J. Org. Chem.* 2003, 68, 9453.
47. Kale B Y, Shinde A D, Sonar S S, Shingate B B, Kumar S, Ghosh S, Venugopal S, Shingare M S. *Beilstein J Org Chem.* 2009, 5:80. doi: 10.3762/bjoc.5.80.
48. Kurangi, R.; Kinalekar, S.; Tilve, S.; Kirtany, J. *ARKIVOC* 2008 (xii), 256.
49. (a) Kumar, A. S.; Ghosh, S.; Soundararajan, R.; Mehta, G. N. *ARKIVOC* 2009 (xii) 173. (b) Kumar, A. S.; Ghosh, S.; Soundararajan, R.; Mehta, G. N. *Synth. Comm.* 2010, 40, 1588.
50. Klumpp, D. A.; Sanchez, G. V. Jr.; Aguirre, S. L.; Zhang, Y.; Leon, de S. *J. Org. Chem.* 2002, 67, 5028.