Tetrahedron Letters 50 (2009) 2140–2143

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chemically-enabled synthesis of 1,2,3,4-tetrahydroisoquinolin-1-ones

Paul S. Humphries *, Gayatri Balan, Bruce M. Bechle, Edward L. Conn, Kenneth J. Dirico, Yu Hui, Robert M. Oliver, James A. Southers, Xiaojing Yang

Pfizer Global R&D, CVMED Chemistry, Eastern Point Road, Groton, CT 06340, USA

ARTICLE INFO

Article history:
Received 5 February 2009
Accepted 20 February 2009
Available online 25 February 2009

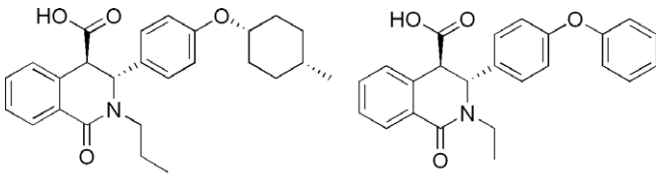
ABSTRACT

We have developed a number of efficient protocols for the facile synthesis of 1,2,3,4-tetrahydroisoquinolin-1-ones. This synthetic methodology allowed concise and efficient exploration of the SAR in all areas of the molecule. A number of these methods proved to be versatile, efficient and amenable to parallel synthesis.

G protein-coupled receptor 40 (GPR40) belongs to a family of fatty acid (FA) binding GPCRs, which include GPR40, GPR41, GPR43, and GPR120.[1] GPR41 and GPR43 are activated by short-chain FAs, GPR40 is activated by medium- and long-chain FAs, and GPR120 is activated by long-chain FAs.[2] GPR40 is highly expressed in pancreatic β-cells and insulin-secreting cell lines. GPR40-deficient β-cells secrete less insulin in response to FAs, and loss of GPR40 protects mice from obesity-induced hyper-insulinemia, hyperglycemia, and glucose intolerance. Conversely, overexpression of GPR40 in β-cells of mice leads to impaired β-cell function, hyperinsulinemia, and diabetes.[3] These results suggest that GPR40 plays an important role in linking obesity and type 2 diabetes.

As part of an ongoing GPR40 drug discovery program in our laboratories, compounds **1** and **2** were identified from high-throughput screening (HTS) and possessed attractive pharmacological properties as well as structural features amenable to optimization by rapid parallel synthesis (Fig. 1).

We initially wanted to explore the SAR of the terminal cyclohexyl and phenyl moieties of **1** and **2**. In order to do this in an efficient manner, we required a concise synthesis of phenol intermediate **7**. This intermediate was accessed in a straightforward fashion following the five step protocol below (Scheme 1).[4] 4-Benxyloxybenzaldehyde **3** was condensed with propylamine to afford imine **4** in excellent yield. Treatment of imine **4** with homophthalic anhydride resulted in the formation of *cis*-lactam **5** in moderate yield along with minor amounts of *trans*-lactam **6**.[5] The thermodynamically less stable isomer **5** could be epimerized under acidic conditions, resulting in the exclusive formation of *trans*-lactam **6** in excellent yield.[6] Esterification of acid **6** with iodomethane afforded the intermediate methyl ester, which was subsequently debenzylated utilizing boron tribromide to yield the required phenol intermediate **7**.[7]



1 **2**

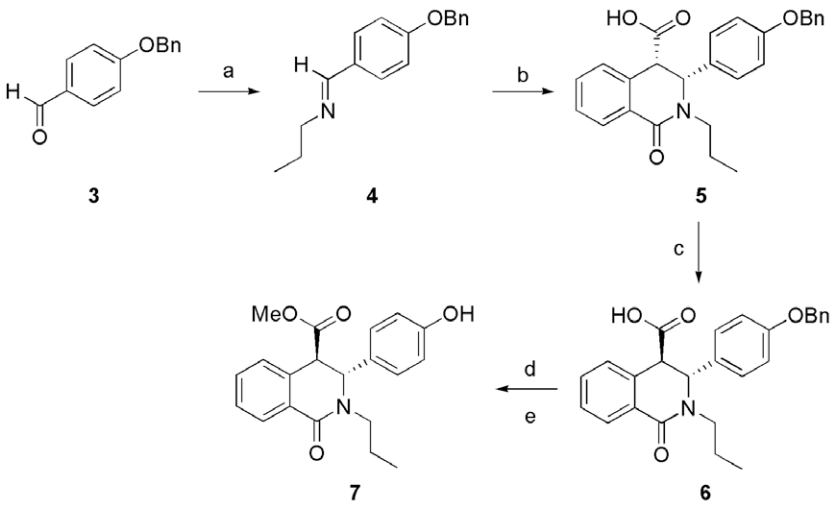
Figure 1. Initial hits **1** and **2** from high-throughput screening.

Our first parallel chemistry effort required a Mitsunobu reaction between phenol **7** and a variety of alkyl alcohols (Scheme 2).[8] This reaction was attempted utilizing polymer-supported triphenylphosphine, but with no success.[9] It was also found that DMF was required as a co-solvent, due to the poor solubility of template **7** in THF alone. Diisopropyl azodicarboxylate (DIAD) was found to be optimal when compared with DEAD, DMAD and PPh_3CN. The resulting products **8** were taken on crude into the ensuing saponification reaction to afford the required acids **9**. In singleton experiments, the crude acids **9** were subjected to an SPE 'catch and release' work-up with SAX cartridges.[10] This work-up allowed for the products to be isolated in pure form, free from any residual DMF solvent or triphenylphosphine oxide by-products. Utilizing this procedure, hit compound **1** was obtained in a 75% yield over the two steps. A small array (~185) of diverse alkyl alcohols were subjected to this synthetic sequence (exchanging a base-acid wash for the SPE work-up) with a 53% success rate.

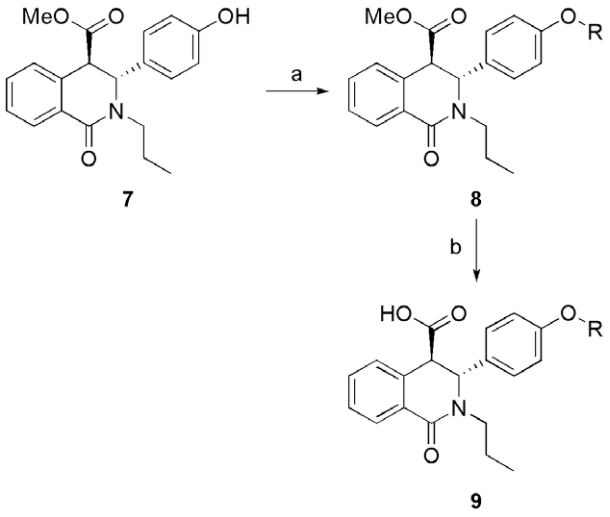
Our next parallel array required a method for obtaining diaryl ethers **11** from phenol **7** (Scheme 3). Utilizing elegant methodology developed in the Evans laboratories, copper-promoted arylation of phenol **7** was carried out with a diverse set of arylboronic acids to yield required products **10**.[11] Once again, the resulting products **10** were taken on crude into the saponification reaction to afford the required acids **11**. Utilizing this methodology, hit compound **2** was obtained in a 71% yield over the two steps. A small array

* Corresponding author. Tel.: +1 860 705 0559.
E-mail address: phumphri@gmail.com (P.S. Humphries).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.157



Scheme 1. Reagents and conditions: (a) $C_3H_7NH_2$, 4 Å MS, CH_2Cl_2, rt, 16 h, 100%; (b) homophthalic anhydride, CH_3CN, 60 °C, 16 h, 50%; (c) AcOH, 120 °C, 16 h, 95%; (d) MeI, K_2CO_3, Me_2CO, rt, 16 h, 90%; (e) BBr_3, CH_2Cl_2, rt, 16 h, 90%.

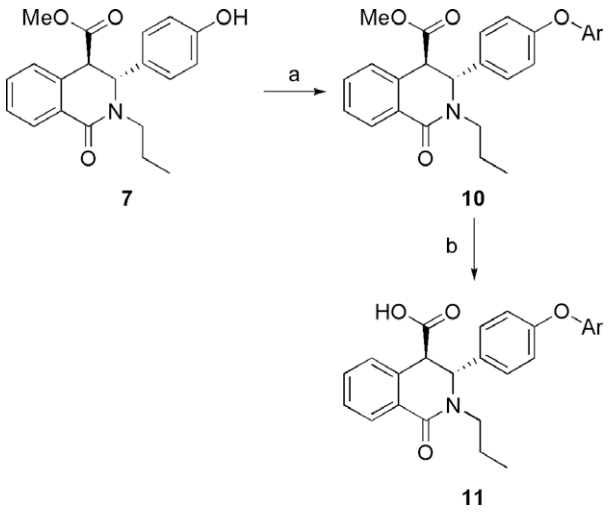


Scheme 2. Reagents and conditions: (a) ROH, PPh_3, DIAD, THF, DMF, 80 °C, 16 h; (b) LiOH, THF, MeOH, H_2O, rt, 16 h.

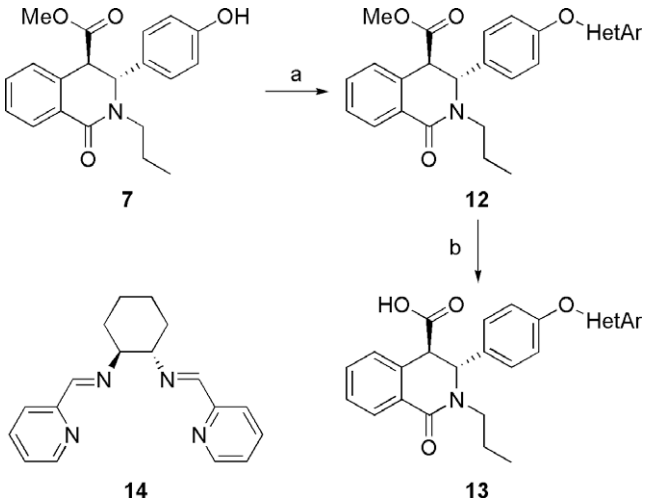
(~110) of diverse arylboronic acids were subjected to this synthetic sequence with a 85% success rate.

The final parallel library to utilize phenol **7** involved S_NAr reactions with 2-bromoheteroaryls to obtain the required products **13** (Scheme 4) This step was optimized under a variety of conditions, utilizing 2-bromopyridine as our partner of choice. Ullman-type coupling of phenol **7**, in the presence of catalyst **14**, afforded **12**, which was saponified to give **13** (where HetAr = 2-pyridyl) in 85% yield.[12] A small array (~20) of 2-bromoheteroaryls were subjected to this synthetic sequence with a 100% success rate.

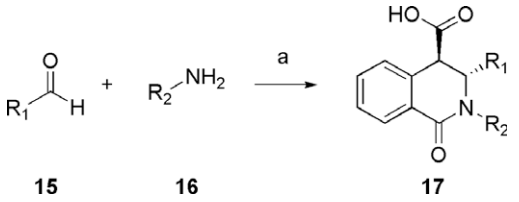
The next endeavor required more diverse SAR exploration of the chemical series (Scheme 5). To achieve this undertaking, we needed to optimize the chemistry in Scheme 1 in order to allow for it to be utilized in a number of parallel arrays. Two of the most immediate challenges were the solubility of the reagents/products in the existing solvents and the requirement for Dean–Stark conditions on formation of the imine (e.g., **4**) Solutions to these challenges involved utilizing conditions similar to reductive aminations by choosing methanol as the solvent of choice for imine formation. The poor solubility of homophthalic anhydride necessitated the use of DMF as the solvent for the formation of the *cis*- and



Scheme 3. Reagents and conditions: (a) $ArB(OH)_2$, $Cu(OAc)_2$, Et_3N, Py, 1,2-DCE, DMF, 4 Å MS, air, 50 °C, 16 h; (b) LiOH, THF, MeOH, H_2O, rt, 16 h.



Scheme 4. Reagents and conditions: (a) 2-Br-HetAr, CuI (cat.), **14** (cat.), K_3PO_4, MeCN, 100 °C, 16 h; (b) LiOH, THF, MeOH, H_2O, rt, 16 h.



Scheme 5. Reagents and conditions: (a) MeOH, rt, 16 h then homophthalic anhydride, DMF, rt, 16 h then 1 N aq NaOH, rt, 16 h.

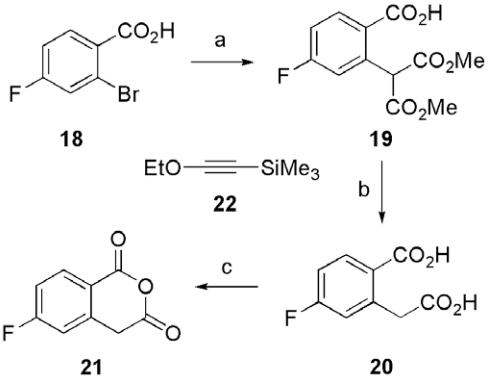
trans-lactams (e.g., **5** and **6**). The resulting mixture was converted to all *trans*-lactam (e.g., **6**) by subjection to strong base, rather than the original acidic conditions. Two libraries were executed utilizing this synthetic sequence with a success rate of 67% (varying R_2) and 71% (varying R_1).

Diversification of the left-hand phenyl ring required an efficient synthesis of diverse homophthalic anhydrides. A representative synthetic scheme from this exercise is shown below (Scheme 6). Acid **18** was subjected to copper-catalyzed coupling with the anion of dimethyl malonate to afford diester **19**, which was taken on crude. Decarboxylation of **19** was achieved under acidic conditions to yield required bis-acid **20** in moderate yield over two steps.[13] Dehydrative cyclization of **20**, utilizing **22**,[14] resulting in the efficient formation of anhydride **21** in excellent yield.[15] Attempts to achieve this transformation utilizing acetyl chloride,[16] acetic anhydride,[17] or thionyl chloride[18] resulted in lower yields. A number of other substituted anhydrides were also synthesized in a similar fashion.

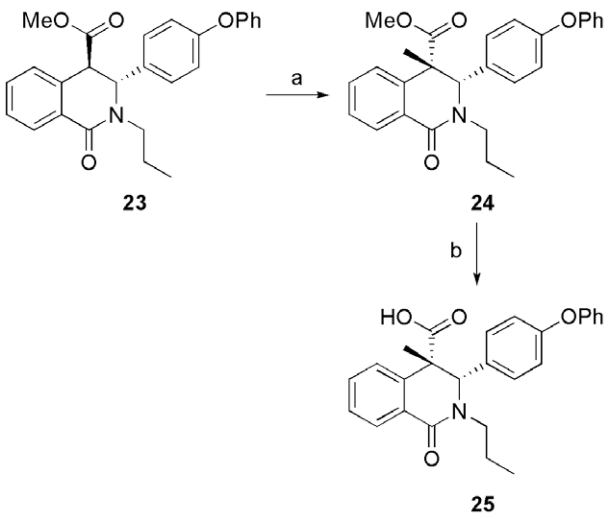
SAR exploration also required us to synthesize the α-methylcarboxylic acid **25** and it's diastereomer **30**. Intermediate ester **23** (obtained via Scheme 5) was deprotonated and the resulting enolate was subjected to iodomethane to afford the single diastereomer **24** in 92% yield. Relative stereochemistry was confirmed by the observed NOE (2.5%) between the C-3 methine and the C-4 methyl group. This facial selectivity is also in line with that reported by others.[19] Saponification of **24** yielded required acid **25** in a straightforward fashion (Scheme 7).

Due to the complete facial selectivity in the formation of **24**, access to diastereomer **30** required the synthesis of anyhdride **29** (Scheme 8). Esterification of bis-acid **26** afforded bis-ester **27**. Deprotonation of **27**, treatment of the resulting enolate with iodomethane, followed by saponification afforded **28** in good yield.[20] Dehydrative cyclization, utilizing **22**, occurred in moderate yield to form required anyhdride **29**.

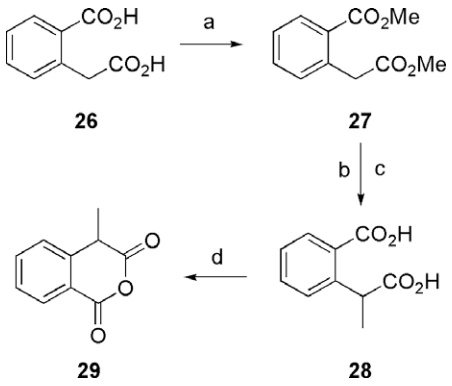
Formation of the imine from 4-phenoxybenzaldehyde and propylamine, followed by treatment with anyhdride **29** afforded a mixture of two diastereomers **30** and **25**. ^{1}H NMR analysis of the crude reaction mixture revealed a ratio of 1.4–1.7:1 favoring diastereomer **30**, which was isolated in 25% yield. Diastereomer **25** was found to be



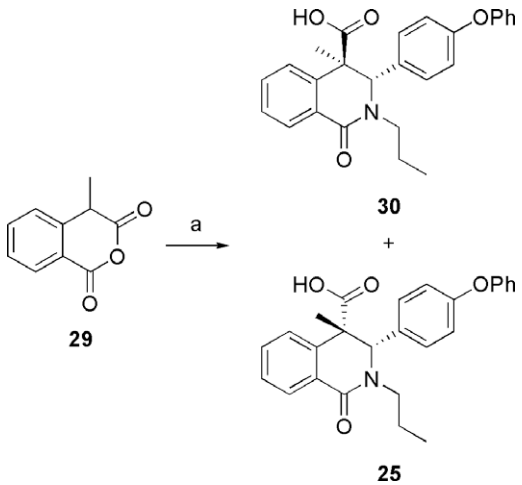
Scheme 6. Reagents and conditions: (a) NaH, $CuBr_2$ (cat.), $CH_2(CO_2Me)_2$, 70 °C, 2 h; (b) HCl, 110 °C C, 48 h, 50% (two steps); (c) **22**, CH_2Cl_2, rt, 1 h, 93%.



Scheme 7. Reagents and conditions: (a) LDA, THF, −78 °C, MeI, 20 min, 92%; (b) LiOH, THF, MeOH, H_2O, rt, 16 h, 95%.



Scheme 8. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, 1,4-dioxane, 70 °C, 16 h, 87%; (b) LDA, THF, −78 °C, MeI, HMPA, 30 min, 75%; (c) LiOH, 1,4-dioxane, MeOH, H_2O, 50 °C, 16 h, 62%; (d) **22**, CH_2Cl_2, rt, 1 h, 52%.



Scheme 9. Reagents and conditions: (a) 4-phenoxybenzaldehyde, propylamine, MeOH, rt, 16 h then **29**, DMF, rt, 16 h, **30** = 25% and **25** = 17%.

identical to that obtained by the method in Scheme 7. Unlike **25**, diastereomer **30** showed no observable NOE between the C-3 methine and the C-4 methyl group (Scheme 9).

In summary, we have developed a number of efficient protocols for the facile synthesis of 1,2,3,4-tetrahydroisoquinolin-1-ones. This synthetic methodology allowed concise and efficient exploration of the SAR in all areas of the molecule. A number of these methods proved to be versatile, efficient and amenable to parallel synthesis.

Acknowledgements

The authors would like to thank Chris Limberakis for stimulating discussions and feedback on this manuscript.

References and notes

1. (a) Hirasawa, A.; Hara, T.; Katsuma, S.; Adachi, T.; Tsujimoto, G. *Biol. Pharm. Bull.* **2008**, *31*, 1847; (b) Bernard, J. *Curr. Opin. Inv. Drugs* **2008**, *9*, 1078; (c) Telvekar, V. N.; Kundaikar, H. S. *Curr. Drug Targets* **2008**, *9*, 899; (d) Costanzi, S.; Neumann, S.; Gershengorn, M. C. *J. Biol. Chem.* **2008**, *283*, 16269; (e) Winzell, M. S.; Ahren, B. *Pharmacol. Ther.* **2007**, *116*, 437; (f) Rayasam, G. V.; Tulasi, V. K.; Davis, J. A.; Bansal, V. S. *Exp. Opin. Ther. Targets* **2007**, *11*, 661.
2. (a) Briscoe, C. P.; Tadayyon, M.; Andrews, J. L.; Benson, W. G.; Chambers, J. K.; Eilert, M. M.; Ellis, C.; Elshourbagy, N. A.; Goetz, A. S.; Minnick, D. T.; Murdock, P. R.; Sauls, H. R.; Shabon, U.; Spinage, L. D.; Strum, J. C.; Szekeres, P. G.; Tan, K. B.; Way, J. M.; Ignar, D. M.; Wilson, S.; Muir, A. I. *J. Biol. Chem.* **2003**, *278*, 11303; (b) Itoh, Y.; Kawamata, Y.; Harada, M.; Kobayashi, M.; Fujii, R.; Fukusumi, S.; Ogi, K.; Hosoya, M.; Tanaka, Y.; Uejima, H.; Tanaka, H.; Maruyama, M.; Satoh, R.; Okubo, S.; Kizawa, H.; Komatsu, H.; Matsumura, F.; Noguchi, Y.; Shinohara, T.; Hinuma, S.; Fujisawa, Y.; Fujino, M. *Nature* **2003**, *422*, 173; (c) Brown, A. J.; Goldsworthy, S. M.; Barnes, A. A.; Eilert, M. M.; Tcheang, L.; Daniels, D.; Muir, A. I.; Wigglesworth, M. J.; Kinghorn, I.; Fraser, N. J.; Pike, N. B.; Strum, J. C.; Steplewski, K. M.; Murdock, P. R.; Holder, J. C.; Marshall, F. H.; Szekeres, P. G.; Wilson, S.; Ignar, D. M.; Foord, S. M.; Wise, A.; Dowell, S. J. *J. Biol. Chem.* **2003**, *278*, 11312.
3. Steneberg, P.; Rubins, N.; Bartoov-Shifman, R.; Walker, M. D.; Edlund, H. *Cell Metab.* **2005**, *1*, 245.
4. All new compounds were characterized by full spectroscopic data, yields refer to chromatographed material with purity >95%.
5. (a) Ryckebusch, A.; Garcin, D.; Lansiaux, A.; Goossens, J.-F.; Baldeyrou, B.; Houssin, R.; Bailly, C.; Henichart, J.-P. *J. Med. Chem.* **2008**, *51*, 3617; (b) Morrell, A.; Placzek, M.; Parmley, S.; Antony, S.; Dexheimer, T. S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2007**, *50*, 4419; (c) Ng, P. Y.; Tang, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5352; (d) Morrell, A.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2006**, *49*, 7740.
6. (a) Cushman, M.; Gentry, J.; Dekow, F. *J. Org. Chem.* **1977**, *42*, 1111; (b) Cushman, M.; Mohan, P. *Tetrahedron Lett.* **1985**, *26*, 4563.
7. Paliakov, E.; Strekowski, L. *Tetrahedron Lett.* **2004**, *45*, 4093.
8. (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380; (b) Mitsunobu, O. *Synthesis* **1981**, 1; (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335; (d) Hughes, D. L. *Org. Prep. Proc. Int.* **1996**, *28*, 127.
9. Humphries, P. S.; Do, Q.-Q. T.; Wilhite, D. M. *Beilstein J. Org. Chem.* **2006**, *2*, 21.
10. Isolute SAX cartridges were purchased from Biotage AB (www.biotage.com).
11. (a) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937; (b) Decicco, C. P.; Song, Y.; Evans, D. A. *Org. Lett.* **2001**, *3*, 1029.
12. Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913.
13. Alcaraz, L.; Furber, M.; Purdie, M.; Springthorpe, B. WO 2003/068743 A1, 2003; *Chem. Abstr.* **2003**, *139*, 197375.
14. Evans, D. A.; Janey, J. M. *Org. Lett.* **2001**, *3*, 2125.
15. Lio, K.; Ramesh, N. G.; Okajima, A.; Higuchi, K.; Fujioka, H.; Akai, S.; Kita, Y. *J. Org. Chem.* **2000**, *65*, 89.
16. (a) Tsou, H.-R.; Otteng, M.; Tran, T.; Floyd, M. B.; Reich, M.; Birnberg, G.; Kutterer, K.; Ayral-Kaloustian, S.; Ravi, M.; Nilakantan, R.; Grillo, M.; McGinnis, J. P.; Rabindran, S. K. *J. Med. Chem.* **2008**, *51*, 3507; (b) Vankatram, A.; Colley, T.; DeRuiter, J.; Smith, F. *J. Het. Chem.* **2005**, *42*, 297.
17. (a) Bauta, W. E.; Lovett, D. P.; Cantrell, W. R.; Burke, B. D. *J. Org. Chem.* **2003**, *68*, 5967; (b) Bauta, W. E.; Cantrell, W. R.; Lovet, D. P. WO 2003/004486 A2, 2003; *Chem. Abstr.* **2003**, *138*, 106599.
18. Oezcan, S.; Balci, M. *Tetrahedron* **2008**, *64*, 5531.
19. Xiao, X.; Miao, Z.-H.; Antony, S.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2795.
20. (a) Kita, Y.; Akai, S.; Ajimura, N.; Yoshigi, M.; Tsugoshi, T.; Yasuda, H.; Tamura, Y. *J. Org. Chem.* **1986**, *51*, 4150; (b) Yamaguchi, M.; Hasebe, K.; Higashi, H.; Uchida, M.; Irie, A.; Minami, T. *J. Org. Chem.* **1990**, *55*, 1611.