Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 3744–3748
Tetrahedron Letters

Acyloins from Morita–Baylis–Hillman adducts: an alternative approach to the racemic total synthesis of bupropion

Giovanni W. Amarante, Patrícia Rezende, Mayra Cavallaro, Fernando Coelho *

Laboratory of Synthesis of Natural Products and Drugs, DQO/IQ/Unicamp, PO Box 6154, 13084-971 Campinas, SP, Brazil

Received 8 February 2008; revised 4 April 2008; accepted 7 April 2008
Available online 10 April 2008

Abstract

In this Letter, we describe an easy and straightforward strategy for the preparation of acyloins (α-hydroxyketones) from Morita–Baylis–Hillman adducts, based on a Curtius rearrangement. Different acyloins were obtained with good overall yield (>40% for three steps). To exemplify the synthetic usefulness of this strategy, total synthesis of (±)-bupropion, a dopamine, and nor-epinefrine reuptake inhibitor has been accomplished in eight steps with an overall yield of 25%.

Acyloins or α-hydroxyketones are a functional group that plays an important role in organic synthesis. This structural moiety is widespread in compounds of natural origin as well as in advanced intermediates en route different target molecules.[1,2] The anti-inflammatory agent cortisone acetate (**1**), the anti-cancer agents daunorubicin and daunomycinone (**2** and **3**),[3] the natural flavouring agents (**4** and **5**),[4] or the male pheromone compounds of the longhorn beetles *Hylotropus bajulus* ('old-house borer') (**6** and **7**)[5] are examples of drugs or biologically active compounds which present the acyloin moiety in their structures (Fig. 1).

The biological, synthetic, and commercial relevancies of acyloins have motivated the development of different approaches to synthesize them, both in racemic and enantioselective pure forms. Conventionally, α-hydroxy ketones are prepared by the acyloin condensation reaction,[6] oxidation of enolates,[7] or reduction of α-diketones or esters.[1,8] Recently, a method based on ketohydroxylation of alkenes was developed to afford acyloins.[7c,9] Alternatively, radical oxidation of a 1,3-dicarbonyl compound with cerium salt could also be used as a method for the preparation of acyloins.[10] Most recently, a skeletal rearrangement of symmetrically α,α-disubstituted α-amino aldehyde has been reported as an elegant new strategy for preparing acyloins.[11]

Morita–Baylis–Hillman (MBH) is an exquisite organic chemical transformation which provides highly functionalized carbonyl compounds.[12] The resulted MBH adducts have found vast application as a versatile building block to generate either bioactive compounds[13] or useful synthetic intermediates.[14]

We have been involved in a research program aimed at the synthesis of some oxazolidinones with anti-microbial properties from MBH adducts.[13b] To obtain the desired oxazolidinones we decided to prepare ene-carbamates from MBH adducts and use them as a substrate for the synthesis of the required oxazolidinones, via a nucleophilic attack of an alkoxy ion on the carbonyl group of the ene-carbamate. The most direct way to prepare the latter was via a Curtius rearrangement of a hydrolyzed MBH adduct, followed by the treatment of the intermediate ene-isocyanate with an alcohol (methanol or *t*-butanol). During the preparation of the required ene-carbamates we have observed the formation of an acyloin as a byproduct. The acyloin was likely formed due to the presence of water in the alcohol used to transform the ene-isocyanate into the corresponding ene-isocarbamate.

* Corresponding author. Tel.: +55 19 3521 3085; fax: +55 19 3521 3023.
E-mail address: coelho@iqm.unicamp.br (F. Coelho).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.040

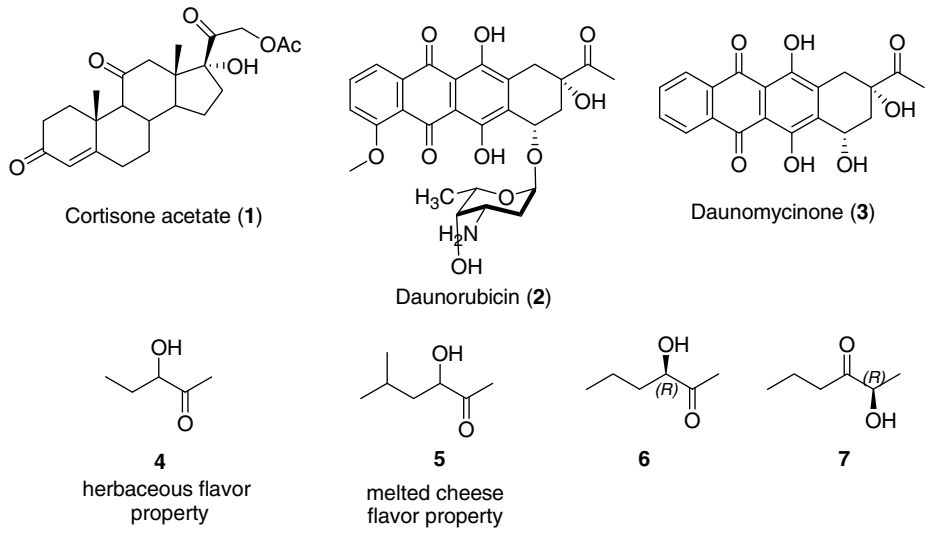


Fig. 1. Some examples of biologically active compounds presenting the acyloin moiety in their structures.

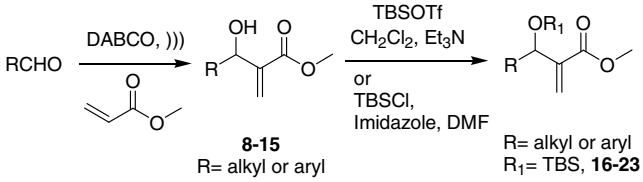
The importance of acyloins in natural products chemistry and organic synthesis calls for the availability of as many alternative methods to prepare these key compounds as possible. Thus we decided to systematically check the possibility of preparing acyloins from MBH adducts. We disclose herein our results on the utilization of MBH adducts as substrates for the synthesis of acyloins. The synthetic usefulness of this new acyloin preparation method was demonstrated by performing the total synthesis of (±)-buproprion.

The MBH adducts were prepared according to a methodology we described some years ago.[15] Assuming an increase of the polarity of the ene-isocyanates, which could make the isolation procedure difficult, the MBH adducts were transformed into the corresponding silyl ethers by the treatment of the MBH adducts with TBSCl or TBSOTf. Results from the preparation of MBH adducts as well as those referring to the protective step are summarized in Table 1.

Having all silylated Morita–Baylis–Hillman adducts in hand, we submitted them to an ester group hydrolysis, in order to obtain the acids which would be used as substrates for the Curtius rearrangement step. Then, the silylated MBH **16**–**23** were treated with LiOH in a mixture of CH_3CN–H_2O(1:1), at 50–60 °C, to afford the acids with almost quantitative yields. The only exception was the hydrolysis of the silylated ester **16**. In this particular case we obtained a yield of only 91%. Likely this yield is due to the fact that the acid derived from **16** is a small polar molecule with a good water solubility, despite the presence of the TBS group in its structure.

Acids **24**–**31** were submitted to the Curtius rearrangement.[16] Thus they were reacted initially with chloroethyl formate at 5 °C in the presence of triethylamine for 5 min, followed by a treatment with NaN_3 to provide the intermediate acylazides.

Table 1
Preparation of the protected MBH adducts

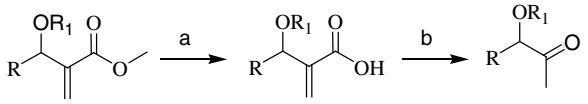


Entry	R	MBH[a,b,c] (%)	Protected adduct[b,c] (%)
1	H	**8**, 70	**16**, 67[d]
2	Hexyl	**9**, 76	**17**, >99[e]
3	Phenyl	**10**, 75	**18**, >99[e]
4	4-CH_3O-Phenyl	**11**, 73	**19**, >99[e]
5	3-Cl-Phenyl	**12**, 89	**20**, >99[e]
6	Thiazolyl	**13**, 98	**21**, >99[d]
7	2-O_2N-Phenyl	**14**, 99	**22**, 97[e]
8	Thiophene	**15**, 90	**23**, 90[d]

[a] The Morita–Baylis–Hillman reactions were performed using methyl acrylate as solvent in an ultrasonic bath (1000 W, 40 Hz).
[b] The yield refers to isolated and purified product.
[c] All spectral data for each compound are compatible to data available in the literature.[16]
[d] TBSOTf is used as silylating reagent.
[e] TBSCl is used as silylating reagent.

After solvent removal, acylazides were thermally rearranged by refluxing them in toluene for 2 h to afford the ene-isocyanates. The entire sequence of reactions was performed without any purification steps.[17] The only procedure used between each step was simply solvent removal. After evaporation, the crude ene-isocyanates were refluxed in water. To our delight, after 12 h the acyloins were smoothly formed with very good overall yields. In Table 2 we summarize the entire sequence as well as the overall yield obtained in the preparation of the acyloins from the silylated acids **24**–**31**.

Table 2
Preparation of acyloins from MBH adducts



16-23
R= alkyl or aryl
R_1= TBS

24-31
MBH acids

32-39
Acyloins

Reagents and conditions: (a) LiOH, CH_3CN:H_2O (1:1), 50–60 °C, 2 h⟶4 h, >99%; (b) (i) $ClCO_2Et$, 5 °C, 5 min; (ii) NaN_3, rt, 2 h; (iii) $PhCH_3$, reflux, 2 h; (iv) H_2O, reflux, 12 h (for overall yields see table).

Entry	Protected MBH adducts	Acyloins[a,b,c] (%)
1	**16**, R = H	**32**, 57
2	**17**, R = Hexyl	**33**, 42
3	**18**, R = Phenyl	**34**, 50
4	**19**, R = 4-CH_3O-Phenyl	**35**, 48
5	**20**, R = 3-Cl-Phenyl	**36**, 45
6	**21**, R = Thiazolyl	**37**, 43
7	**22**, R = 2-O_2N-phenyl	**38**, 46
8	**23**, R = Thiophene	**39**, 44

[a] The yields refer to isolated and purified products.
[b] Yields for three steps (including the protection step).
[c] All spectroscopic data are compatible with the proposed structures.[17]
For a mechanism proposal see Reference section.[18]

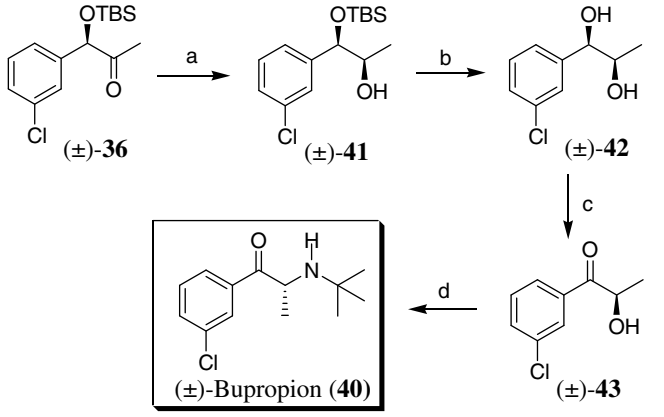
In all cases the acyloins were obtained in good overall yield from the silylated MBH adducts. For all cases the yield for each step is good (≈75–80% for each step). Different types of acyloins were obtained and the method proved to be quite general. Even heterocyclic MBH adducts (Table 2, entries 6 and 8) provide the corresponding acyloins with good overall yields. The method is very simple and could be easily performed without the need of using any critical experimental conditions.

Tobacco addiction is a very serious health problem all over the world. Unfortunately, the diseases associated with the smoking habit (lung cancer, pulmonar emphysema, and cardiovascular problems) have a severe negative impact on the public health system of the majority of western world countries.

Due to the gravity of the health problem caused by tobacco addiction there are several types of medical and behavioral therapies to circumvent and cure this addiction. Most recently, the elucidation of the biochemical mechanisms used by the human brain to develop addiction has permitted the development of some efficient chemical substances which can effectively aid addiction treatment.[19]

Among these substances bupropion [(±)-α-*t*-butylamino 3-chloropropiophenone] (**40**, Scheme 1) has an important role. This compound is a potent inhibitor of dopamine reuptake with subtle noradrenergic reuptake also.[20] Bupropion is an atypical antidepressant, which has been licensed by FDA to treat the smoker's abstinence syndrome.[21]

Owing to the pharmacological importance of bupropion, several approaches to synthesize it have already been developed.[22] Bupropion is administered in its racemic form, since it racemizes very quickly in the body when administered in its enantiomerically pure form.



Scheme 1. Total synthesis of (±)-bupropion from an acyloin prepared from an MBH adduct. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, quantitative yield; (b) TBAF/THF, rt, 2 h, 97%; (c) IBX, DMSO, rt, 30 h, 85%; (d) (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, −40 °C, 30 min; (ii) *t*-$BuNH_2$, 12 h, 75%.

The pharmaceutical importance of bupropion (**40**), associated with our will of demonstrating the usefulness of the method we have just developed for the preparation of acyloins from MBH adducts stimulated us to propose a new approach for the racemic total synthesis of **40**.

The silylated acyloin **36** was used as substrate for our synthesis. Thus, α-hydroxy ketone **36** was reduced with $NaBH_4$ in methanol to furnish the mono-silylated diol **41** in quantitative yield. Treatment of **41** with TBAF in THF gave diol **42** in 97% yield (*syn* as major isomer—2.5:1). In this stage of the synthesis, it was necessary to regioselectively oxidize diol **42** to prepare the regioisomeric acyloin **43**. We tried several different experimental conditions, however, the only successful one was that in which IBX was used as an oxidizing agent. Thus acyloin **43** was obtained in 85% yield after 30 h at room temperature. Finally, the regioisomeric acyloin **43** was treated with triflic anhydride and 2,6-lutidine in dichloromethane at −40 °C to give a triflate intermediate that was then submitted in situ to a nucleophilic substitution reaction using *t*-butylamine as nucleophile, to afford bupropion (**40**) in 75% yield (for the two steps) (Scheme 1).

In summary, this study clearly demonstrates that Morita–Baylis–Hillman adducts coming from both aliphatic and aromatic aldehydes provide easy access to acyloins, which are valuable intermediates in organic synthesis. The total synthesis of (±)-bupropion has been accomplished in eight steps with an overall yield of 25% using an acyloin prepared by the new strategy disclosed in this Letter. As far as we know this is the first report relating the preparation of acyloins from MBH adducts.

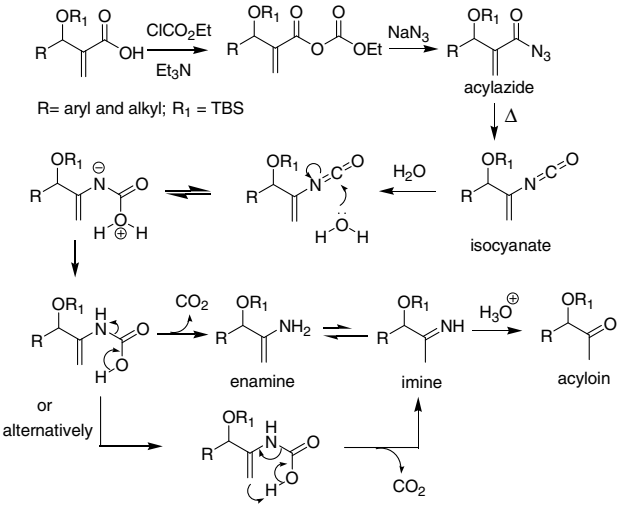
An asymmetric version of this approach could easily be developed simply by using chiral Morita–Baylis–Hillman adducts. Further studies aiming at the development of an asymmetric version of this method, as well as its application for the synthesis of natural products and commercially valuable intermediates, are ongoing in our laboratory and will be reported in due time.

Acknowledgments

We thank the Brazilian science foundations for supporting this work. More specifically G.W.A, P.R., and M.C. thank Fapesp (05/02373-2, 02/07659-3, and 07/55548-0) for fellowships. F.C. thanks Fapesp for a research Grant (06/06347-9) and CNPq for a research fellowship (301832/2007-2). The authors are grateful to Professors Carol H. Collins and Marcos N. Eberlin for helpful suggestions on English grammar and style.

References and notes

1. Khan, F. A.; Dash, J.; Sahu, N.; Gupta, S. *Org. Lett.* **2002**, *4*, 1015–1018 and references cited therein.
2. Scheid, G.; Kuit, W.; Ruijter, E.; Orru, R. V. A.; Henke, E.; Bornscheuer, U.; Wessjohann, L. A. *Eur. J. Org. Chem.* **2004**, 1063–1074.
3. (a) Arcamone, F. *Cancer Res.* **1985**, *45*, 5895–5899; (b) Gottesman, M. M. *Cancer Res.* **1993**, *53*, 747–754; (c) Kaye, S. B. *Br. J. Cancer* **1988**, *58*, 691–694; (d) Monneret, C. *Eur. J. Med. Chem.* **2001**, *36*, 483–493.
4. Neuser, F.; Zorn, H.; Beger, R. G. *J. Agric. Food Chem.* **2000**, *48*, 6191–6195.
5. Schröder, F.; Fettköther, R.; Noldt, U.; Dettner, K.; König, W. A.; Francke, W. *Liebigs Ann. Chem.* **1994**, 1211–1218.
6. (a) Schräpler, U.; Rühlmann, K. *Chem. Ber.* **1964**, *97*, 1383 –1389; (b) Mori, K.; Nakahara, T.; Nozaki, H. *Can. J. Chem.* **1969**, *47*, 3266–3269; For an example of a benzoin type reaction catalyzed by nucleophilic carbene for the preparation of cyclic acyloin, see: (c) Enders, D.; Niemeier, O. *Synlett* **2004**, 2111–2114; (d) Heck, R.; Henderson, A. P.; Köhler, B.; Rétey, J.; Golding, B. T. *Eur. J. Org. Chem.* **2001**, 2623–2627; (e) Greene, A. E.; Coelho, F.; Depres, J.-P. *J. Org. Chem.* **1985**, *50*, 1973–1975.
7. For a comprehensive review on α-hydroxylations up to 1995 see: (a) Davis, F. A.; Chen, B.-C. In *Houben-Weyl Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, New York, 1996; E 21, p 4497; (b) Zhou, P.; Chen, B. A.; Davies, F. A. In *Asymmetric Oxidation Reactions*; Katsuki, T., Ed.; Oxford University Press: Oxford, 2001; p 128; (c) Plietker, B. *Tetrahedron: Asymmetry* **2005**, *16*, 3453–3459.
8. (a) Hayakawa, R.; Sahara, T.; Shimizu, M. *Tetrahedron Lett.* **2000**, *41*, 7939–7941; (b) Bornemann, S.; Crout, D. H. G.; Dalton, H.; Kren, V.; Lobell, M.; Dean, G.; Thomson, N.; Turner, M. M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 425–430; (c) Kawai, Y.; Hida, K.; Tsujimoto, M.; Kondo, S.; Kitano, K.; Nakamura, K.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 99–102.
9. (a) Plietker, B. *Org. Lett.* **2004**, *6*, 289–291; (b) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287–8296; (c) Zhang, Y.; Shen, Z.; Tasng, J.; Zhang, Y.; King, L.; Zhang, Y. *Org. Biomol. Chem.* **2004**, *4*, 1478–1482.
10. Christoffers, J.; Werner, T.; Under, S.; Frey, W. *Eur. J. Org. Chem.* **2003**, 425–431.
11. (a) Ooi, T.; Ohmatsu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 2410–2411; (b) Ooi, T.; Sasito, A.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 3220–3221.
12. (a) Basavaiah, D.; Rao, A. J.; Satyanarayama, T. *Chem. Rev.* **2003**, *103*, 811–891; (b) Almeida, W. P.; Coelho, F. *Quim. Nova* **2000**, *23*, 98–105 (*C. A.* **2000**, *132*, 236562e); (c) Santos, L. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4330–4333; (d) Aggarwal, V. K.; Fulford, S. Y.; Llyod-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706–1708; (e) Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513–15525.
13. (a) Silveira, G. P. C.; Coelho, F. *Tetrahedron Lett.* **2005**, *46*, 6477–6481; (b) Coelho, F.; Rossi, R. C. *Tetrahedron Lett.* **2002**, *43*, 2797–2800; (c) Gowrisankar, S.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 4859–4863; (d) Santos, L. S.; da Silveira Neto, B. A.; Consorti, C. S.; Pavam, C. H.; Almeida, W. P.; Coelho, F.; Eberlin, M. N.; Dupont, J. *J. Phys. Org. Chem.* **2006**, *19*, 731–735.
14. (a) Abella, C. A. M.; Rezende, P.; Souza, M. F. L.; Coelho, F. *Tetrahedron Lett.* **2008**, *49*, 145–148; (b) Mateus, C. R.; Coelho, F. *J. Braz. Chem. Soc.* **2005**, *16*, 386–396; (c) Reddy, L. R.; Fournier, J.-F.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *7*, 2699–2701; (d) Porto, R. S.; Coelho, F. *Synth. Commun.* **2004**, *34*, 3037–3046; (e) Feltrin, M. A.; Almeida, W. P. *Synth. Commun.* **2003**, *33*, 1141–1146; (f) Dunn, P. J.; Fournier, J.-F.; Hughes, M. L.; Searle, P. M.; Wood, A. S. *Org. Process Res. Dev.* **2003**, *7*, 244–253; (g) Masunari, A.; Trazzi, G.; Ishida, E.; Coelho, F.; Almeida, W. P. *Synth. Commun.* **2001**, *31*, 2127–2136.
15. (a) Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopes, E. C. S.; Silveira, G. P. C.; Rossi, R. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437–7447; (b) Almeida, W. P.; Coelho, F. *Tetrahedron Lett.* **1998**, *39*, 8609–8612.
16. Lebel, H.; Leogane, O. *Org. Lett.* **2006**, *8*, 5717–5720 and references cited therein.
17. *Representative experimental procedure*: To a solution of acid **20** (1 g, 3 mmol) in acetone (15 mL) were added, at 0 °C, ethyl chloroformate (0.44 mL, 4.6 mmol) and triethylamine (0.88 mL, 6.1 mmol). After 5–10 min (analysis by TLC shows the complete disappearance of starting material), sodium azide (0.3 g, 4.6 mmol) was added under strong stirring, and the resulting mixture was stirred strongly for 2 h. After that the solvent was evaporated and the residue was dissolved in toluene (15 mL) and refluxed for 2 h. The solvent was evaporated and the residue was dissolved in distilled water (15 mL) and refluxed for 12 h. After, the aqueous phase was extracted with ethyl acetate and after evaporation the residue was purified by silica gel column chromatography to afford acyloin **36** as a yellow tinged oil. All steps could be easily followed by IR spectroscopy, since the C=O IR absorption of the carbonate, acylazide, and isocyanate are very intense and appear in different regions of the IR spectrum. All spectroscopic data (^{1}H, ^{13}C NMR, HRMS) are compatible with the structures proposed for each compound of this work. Bupropion spectral data: ^{1}H NMR ($CDCl_3$, 250 MHz) δ: 7.92 (m, 4H), 6.11 (q, $J = 7.0$ Hz, 1H), 4.65 (br s, 1H, NH), 1.67 (d, $J = 7.0$ Hz, 3H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ: 195.7, 136, 135.2, 133.5, 130.1, 128.6, 126.5, 71.9, 58.1, 30.3, 17.
18. Acyloins perhaps could be formed by the mechanism shown below:



19. (a) Heidbreder, C. *Eur. J. Pharmacol.* **2005**, *526*, 101–112; (b) Thayer, A. M. *Chem. Eng. News* **2006**, *84*, 21–44.
20. Dir, A.; Kulkarni, S. K. *Eur. J. Pharmacol.* **2007**, *568*, 177–185.

21. Mooney, M. E.; Sofuoglu, M. *Exp. Rev. Neurother.* **2006**, *6*, 965–981.
22. (a) Kelley, J. L.; Musso, D. L.; Boswell, G. E.; Soroko, F. E.; Cooper, B. R. *J. Med. Chem.* **1996**, *39*, 347–349; (b) Musso, D. L.; Mehth, N. B.; Soroko, F. E.; Ferris, R. M.; Hollingsworth, E. B.; Kenney, B. T. *Chirality* **1993**, *5*, 495–500; (c) Musso, D. L.; Mehth, N. B.; Soroko, F. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1–6; (d) Perrine, D. M.; Ross, J. T.; Nervi, S. J.; Zimmerman, R. H. *J. Chem. Educ.* **2000**, *77*, 1479–1480; (e) Fang, Q. K.; Han, Z.; Grover, P.; Kessler, D.; Senanayake, C. H.; Wald, S. A. *Tetrahedron: Asymmetry* **2000**, *11*, 3659–3663.