Natural Product Synthesis

DOI: 10.1002/anie.200703814

# Total Synthesis of Azadirachtin—Finally Completed After 22 Years

Johann Jauch*

azadirachtin · Claisen rearrangement ·
natural products · sigmatropic rearrangement ·
synthetic methods

Many plant species produce limonoids to protect themselves against feeding insects. Such compounds are natural insecticides and are named "feeding deterrents". The neem tree *Azadirachta indica*, mainly found in India, is able to prevent the feeding of more than 200 insect species. It was for this reason that Butterworth and Morgan searched for the substances responsible for this effect. In 1968 they reported on the isolation of a compound from neem seeds that completely inhibits the feeding of the desert locust *Schistocerca gregaria* at concentrations of 1 ng per square centimeter.[1] This compound was named azadirachtin.

First investigations of the structure of azadirachtin were published by Morgan and co-workers.[2] However, only some structural elements and functional groups were reported. In 1975 Nakanishi and co-workers[3] published for the first time a complete structure of azadirachtin, which was modified by Ley and co-workers in 1985.[4] At the end of 1985 Kraus et al. published the new structure **1** (Figure 1) of azadirachtin, which was confirmed at the beginning of 1986 by Ley and co-workers by means of X-ray analysis.[5]

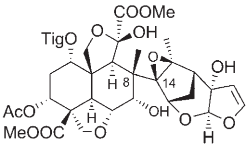


***Figure 1.*** Structure of azadirachtin **1**. Tig = Tigloyl = (*E*)-2-methyl-2-butenoyl.

Azadirachtin possesses 16 stereocenters, 7 quaternary and 9 secondary, as well as 4 different ester groups, 2 hydroxy groups (one belonging to an extremely acid-sensitive hydroxyldihydrofuran ring system), an acid- and base-sensitive semiacetal, and a strained and sterically difficult to access epoxide. This structural complexity and sensitivity of the target molecule makes the total synthesis of azadirachtin an enormous challenge.

The syntheses of complex natural products are nowadays always planned retrosynthetically. The reverse of the retrosynthetic analysis is a synthetic plan, which is followed during the total synthesis.[6] However, by using this method one can never be sure of pitfalls: On the way to the target molecule there may be low-yielding steps, reaction products may have the wrong stereochemistry, or, in the worst case, planned reactions do not work at all. Experienced synthetic chemists often have a "sixth sense" for pitfalls, and they try to prevent such pitfalls by first studying model reactions. However, transferring model studies to the real synthetic challenge may also lead to the above-mentioned difficulties. All these factors make it necessary to rethink and modify the synthetic plan or to develop a completely new strategy.[7]

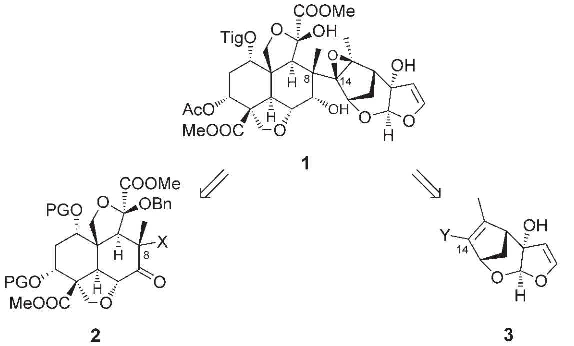
If the biosynthesis of a natural compound is known, one can use it as a basis for the synthetic planning and can try to carry out reactions which are enzyme-catalyzed in nature, and do not use protecting-group strategies, by chemical methods. Such strategies are called biomimetic syntheses.[7a] However, in these cases inefficient reactions can also force the synthetic chemist into detours in the planned synthesis.

Particularly annoying are poor or failing reactions at a late stage of a synthesis. If in such cases the target molecule is readily available from natural sources, difficulties in the total synthesis can be dealt with in two ways. One can try to specifically degrade the natural product to a potential synthetic intermediate and transform this back into the natural product. If this is successful, the last steps in the synthesis have been reliably worked out and further work can focus on the synthesis of the intermediates obtained in the degradation studies. This strategy is called a "relay route" or "relay synthesis".[7a]

Shortly after the correct structure of azadirachtin had been established, Ley and co-workers began their total synthesis of this highly interesting molecule. At first the plan was to synthesize azadirachtin from a suitable decalin fragment **2** (left half) and a suitably functionalized tricyclic hydroxytetrahydrofuran fragment **3** (right half; Scheme 1).[8] This approach necessitates the coupling of two quaternary carbon centers[9] to construct the extremely hindered bond between C8 and C14. In 1994 Ley wrote: "*We recognize this*

---

[*] Prof. Dr. J. Jauch
Universität des Saarlandes
Organische Chemie II
Im Stadtwald 23, 66123 Saarbrücken (Germany)
Fax: (+49) 681-30264151
E-mail: j.jauch@mx.uni-saarland.de

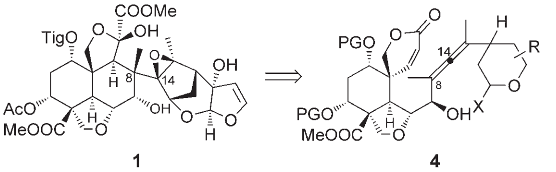


*Scheme 1.* First retrosynthetic disconnection of azadirachtin according to Ley and co-workers. PG = protecting group, Bn = benzyl.

*coupling involves the formation of a difficult bond, but therein lies the challenge*".[10]

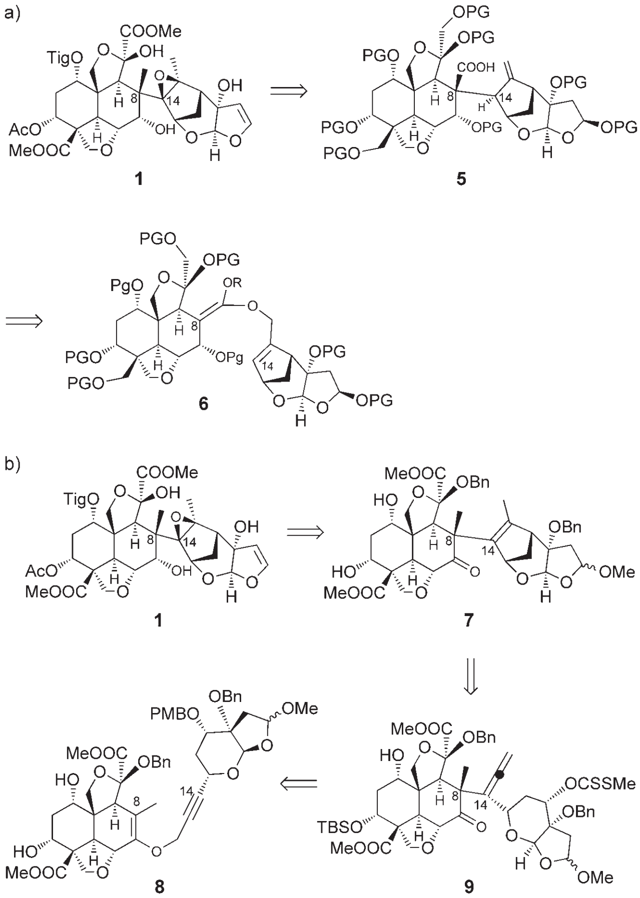
In a series of publications Ley and co-workers[11] reported on the synthesis of variably functionalized left (**2**) and right (**3**) halves of azadirachtin. During this work it became clear that a direct intermolecular coupling of these sterically crowded substructures does not work.[12]

If in a synthetic endeavor one realizes that an *intermolecular* coupling of a crucial bond within the target molecule fails, one can either a) introduce this bond in an earlier step of the synthesis or start from a molecule which already contains this bond or b) connect the two parts through other functional groups which are readily accessible, and then close the desired bond *intramolecularly*. Strategy (a) was favored by Watanabe et al., and was intensively investigated at the time (Scheme 2).[13] In 1999 strategy (b) was chosen independently by the research groups of both Murai[14] and Ley[15] (Scheme 3). The synthetic plan of Nicolaou et al.[16] also corresponds to that strategy (Scheme 4).

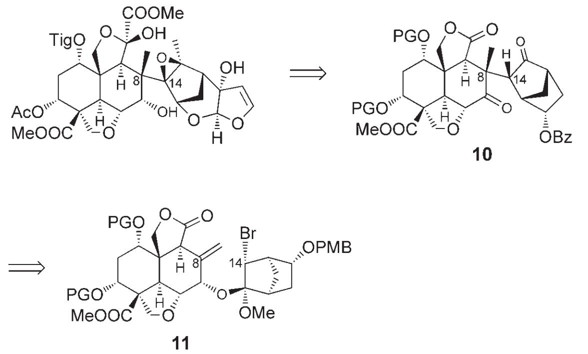


*Scheme 2.* Retrosynthetic disconnection of azadirachtin according to Watanabe et al.

Murai and co-workers used an Ireland–Claisen rearrangement[17] to construct the bond between C8 and C14, and were able to demonstrate its practicability with the model compound **12** (Scheme 5).[14f] Ley et al. focused on a Claisen rearrangement[18] for the coupling of the bond between C8 and C14. Model studies on the Claisen rearrangement showed difficulties with more complex model compounds. For example, model compound **15** could not be converted into **16** in a sealed tube at 165 °C (Scheme 6),[15a] and it was therefore possible that **8** would also not react. Finally, the Claisen rearrangement (**17**→**18**) which had failed under thermal conditions was successfully carried out in yields of 80–88 % under pulsed microwave irradiation (15 × 1 min).[15b] Alternatively, the Claisen rearrangement could be catalyzed by the gold(I) complex $[(Ph_3PAu)_3O]BF_4$.[19] This showed the way to a successful total synthesis of azadirachtin through a Claisen rearrangement of **8** to **19** (Scheme 6).[15c,d]

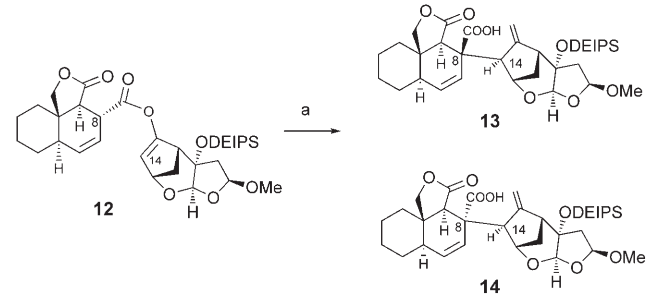


*Scheme 3.* Retrosynthetic analysis of azadirachtin: a) according to Murai and co-workers[14d] and b) according to Ley and co-workers.[15c,d] PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

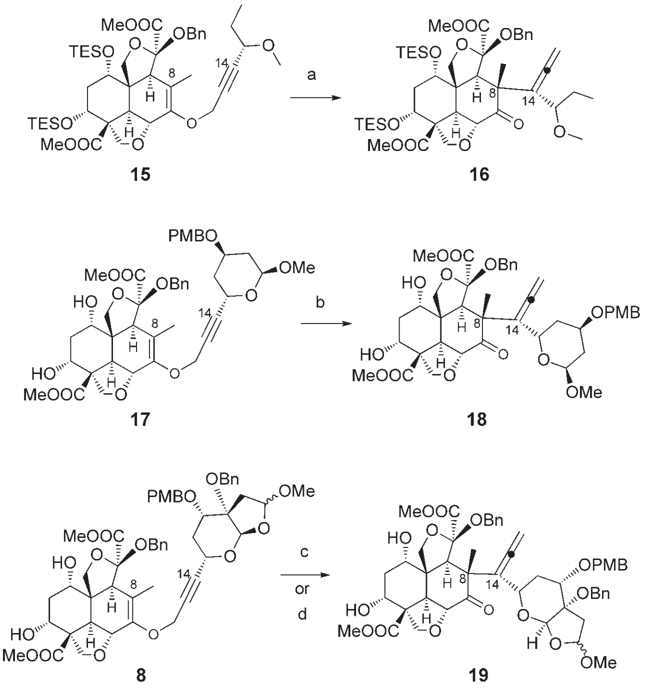


*Scheme 4.* Retrosynthetic disconnection according to Nicolaou et al. Bz = benzoyl.

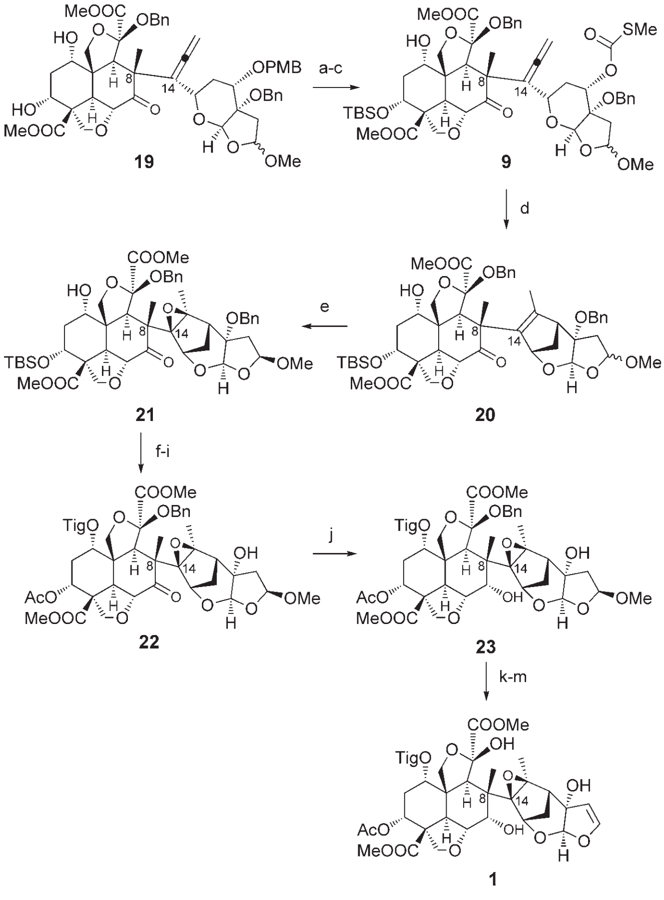
The choice of vinyl propargyl ether **8** for the construction of the C8–C14 bond meant that a route had to be developed for the construction of the tricyclic right half in **19** containing an *endo* methyl group. This task was achieved by Ley and co-workers through a clever radical cyclization with the allene **9**



*Scheme 5.* Ireland–Claisen rearrangement of model compound **12** according to Murai and co-workers. a) $Me_2SiCl_2$, $Et_3N$, LHMDS, toluene, −78 °C to 70 °C. **13**/**14** = 4:1. DEIPS = diethylisopropylsilyl, LHMDS = lithium 1,1,1,3,3,3-hexamethyldisilazide.



*Scheme 6.* Selected Claisen rearrangements from Ley and co-workers. a) Xylene, 165 °C, sealed tube, no reaction; b) 1,2-dichlorobenzene, 180 °C, MWI 15×1 min, 88%; c) 1,2-dichlorobenzene, 185 °C, MWI 15×1 min, 80%; d) $[(Ph_3PAu)_3O]BF_4$, $CH_2Cl_2$, RT, 80%. MWI = Microwave irradiation, TES = triethylsilyl.



*Scheme 7.* Radical cyclization, epoxidation, and completion of the total synthesis of azadirachtin through relay synthesis. a) TBS-imidazole, DMF, 100 °C, 90%; b) DDQ, $CH_2Cl_2$, $H_2O$, RT, 85%; c) $CS_2$, NaHMDS, THF, −78 °C, MeI, −78 °C, 60%; d) $nBu_3SnH$, AIBN, toluene, 100 °C, high dilution, 80%; e) MMPP·$H_2O$, radical scavenger, $NaHCO_3$, MeOH, 105 °C, sealed tube, 7 days, 85% (based on the recovered starting material); f) TBAF, THF, 0 °C, 100%; g) $H_2$/Pd/C, MeOH, RT, 99%; h) $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, RT, 74%; i) tiglinic acid Yamaguchi reagent, $Cs_2CO_3$, toluene reflux, 6 days, 80%; k) $NaBH_4/CeCl_3$, MeOH, 0 °C, 49%; l) $H_2$/Pd/C, MeOH, RT, 81%; m) PhSH, PPTS, $ClCH_2CH_2Cl$, 80 °C, 70%; n) DMDO, $CH_2Cl_2$, −78 °C to RT, then toluene reflux, 67%. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, NaHMDS = sodium 1,1,1,3,3,3-hexamethyldisilazide, AIBN = azobisisobutyronitrile, MMPP = magnesium monoperoxyphthalate, TBAF = tetrabutylammonium fluoride, DMAP = 4-dimethylaminopyridine, PPTS = pyridinium *p*-toluenesulfonate, DMDO = dimethyldioxirane.

(obtained from **19**) (Scheme 7).[15c,d] Epoxidation with magnesium monoperoxyphthalate finally resulted in **21**, which was readily available through relay synthesis and could be transformed into azadirachtin by these authors. The enormous crowding around the C8–C14 bond can be estimated from the reaction conditions necessary for the epoxidation of the double bond in **20**: magnesium monoperoxyphthalate (comparable to *meta*-chloroperbenzoic acid), seven days reaction time at 105 °C (!) with conversions of only 20 to 35%. The unreacted starting material could be almost completely recovered.

The relay synthesis consists of some remarkable steps. Generation of the tiglinic acid ester with the sterically hindered C1-OH group works well with a mixed anhydride of tiglinic acid and 2,4,6-trichlorobenzoic acid (Yamaguchi reagent from tiglinic acid). Reduction of the carbonyl group at C7 with Luche reagent can be carried out chemoselctively but not stereoselectively, and at the end of the relay route to azadirachtin the double bond of the dihydrofuran ring system is established through sulfoxide pyrolysis in boiling toluene (Scheme 7).[15c]

The complete total synthesis contains 71 steps (longest linear sequence 48 steps) and occurs with a total yield of 0.00015%. Finally, after 22 years, S. V. Ley and more than 35 co-workers have for the first time achieved the total synthesis of azadirachtin. A real highlight of organic chemistry!

---

[1] J. H. Butterworth, E. D. Morgan, *Chem. Commun.* **1968**, 23 – 24.

[2] J. H. Butterworth, E. D. Morgan, G. R. Percy, *J. Chem. Soc. Perkin Trans. 1* **1972**, 2445 – 2450.

[3] P. R. Zanno, I. Miura, K. Nakanishi, D. L. Elder, *J. Am. Chem. Soc.* **1975**, *97*, 1975 – 1977.

[4] J. N. Bilton, H. B. Broughton, S. V. Ley, Z. Lidert, E. D. Morgan, H. S. Rzepa, R. N. Sheppard, *J. Chem. Soc. Chem. Commun.* **1985**, 986 – 987.

[5] a) W. Kraus, M. Bokel, A. Klenk, H. Pöhnl, *Tetrahedron Lett.* **1985**, *26*, 6435 – 6438; b) H. B. Broughton, S. V. Ley, A. M. Z. Slawin, D. J. Williams, E. D. Morgan, *J. Chem. Soc. Chem. Commun.* **1986**, 46 – 47.

[6] a) E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**; b) P. Wyatt, S. Warren, *Organic Synthesis*, Wiley, Hoboken, **2007**.

[7] a) K. C. Nicolaou, E. J. Sorensen, *Classics In Total Synthesis I*, Wiley-VCH, Weinheim, **1996**; b) K. C. Nicolaou, S. A. Snyder, *Classics In Total Synthesis II*, Wiley-VCH, Weinheim, **2003**; c) M. A. Sierra, M. C. de la Torre, *Dead Ends and Detours*, Wiley-VCH, Weinheim, **2004**; d) *Strategies And Tactics In Organic Synthesis*, *Vol. 1–6* (Eds.: T. Lindberg, M. Harmata), Elsevier, Dordrecht, **1984–2005**.

[8] See for example: H. C. Kolb, S. V. Ley, *Tetrahedron Lett.* **1991**, *32*, 6187 – 6190.

[9] *Quarternary Stereocenters* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**.

[10] a) H. C. Kolb, S. V. Ley, A. M. Z. Slawin, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735 – 2762; b) S. V. Ley, *Pure Appl. Chem.* **1994**, *66*, 2099 – 2102.

[11] a) S. V. Ley, A. A. Somovilla, H. B. Broughton, D. Craig, A. M. Z. Slawin, P. L. Toogood, D. J. Williams, *Tetrahedron* **1989**, *45*, 2143 – 2164; b) J. C. Anderson, S. V. Ley, D. Santafianos, R. N. Sheppard, *Tetrahedron* **1991**, *47*, 6813 – 6850; c) H. C. Kolb, S. V. Ley, *Tetrahedron Lett.* **1991**, *32*, 187 – 6190; d) H. C. Kolb, S. V. Ley, A. M. Z. Slawin, D. J. Williams, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2735 – 2762; e) W.-J. Koot, S. V. Ley, *Tetrahedron* **1995**, *51*, 2077 – 2090; f) A. A. Denholm, L. Jennens, S. V. Ley, A. Wood, *Tetrahedron* **1995**, *51*, 6591 – 6604.

[12] A successful direct coupling of the two halves had never been published.

[13] a) H. Watanabe, T. Watanabe, K. Mori, *Tetrahedron* **1996**, *52*, 13939 – 13950; b) H. Watanabe, T. Watanabe, K. Mori, T. Kitahara, *Tetrahedron Lett.* **1997**, *38*, 4429 – 4432; c) H. Watanabe, N. Mori, D. Itoh, T. Kitahara, K. Mori, *Angew. Chem.* **2007**, *119*, 1534 – 1538; *Angew. Chem. Int. Ed.* **2007**, *46*, 1512 – 1516.

[14] a) N. Kanoh, J. Ishihara, A. Murai, *Synlett* **1997**, 737 – 739; b) J. Ishihara, T. Fukuzaki, A. Murai, *Tetrahedron Lett.* **1999**, *40*, 1907 – 1910; c) J. Ishihara, Y. Yamamoto, N. Kanoh, A. Murai, *Tetrahedron Lett.* **1999**, *40*, 4387 – 4390; d) N. Kanoh, J. Ishihara, Y. Yamamoto, A. Murai, *Synthesis* **2000**, 1878 – 1893; e) Y. Yamamoto, J. Ishihara, N. Kanoh, A. Murai, *Synthesis* **2000**, 1894 – 1906; f) T. Fukuzaki, S. Kobayashi, T. Hibi, Y. Ikuma, J. Ishihara, N. Kanoh, A. Murai, *Org. Lett.* **2002**, *4*, 2877 – 2880.

[15] a) S. V. Ley, C. E. Gutteridge, A. R. Pape, C. D. Spilling, C. Zumbrunn, *Synlett* **1999**, 1295 – 1297; b) T. Durand-Reville, L. B. Gobbi, B. L. Gray, S. V. Ley, J. S. Scott, *Org. Lett.* **2002**, *4*, 3847 – 3850; c) G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, C. Ayats, S. V. Ley, *Angew. Chem.* **2007**, *119*, 7773 – 7776; *Angew. Chem. Int. Ed.* **2007**, *46*, 7629 – 7632; d) G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. Maslen, S. V. Ley, *Angew. Chem.* **2007**, *119*, 7777 – 7779; *Angew. Chem. Int. Ed.* **2007**, *46*, 7633 – 7635.

[16] a) K. C. Nicolaou, M. Follmann, A. J. Roecker, K. W. Hunt, *Angew. Chem.* **2002**, *114*, 2207 – 2210; *Angew. Chem. Int. Ed.* **2002**, *41*, 2103 – 2106; b) K. C. Nicolaou, A. J. Roecker, M. Follmann, R. Baati, *Angew. Chem.* **2002**, *114*, 2211 – 2214; *Angew. Chem. Int. Ed.* **2002**, *41*, 2107 – 2110; c) K. C. Nicolaou, A. J. Roecker, H. Monenschein, P. Guntupalli, M. Follmann, *Angew. Chem.* **2003**, *115*, 3765 – 3770; *Angew. Chem. Int. Ed.* **2003**, *42*, 3637 – 3642; d) K. C. Nicolaou, P. K. Sasmal, T. V. Koftis, A. Converso, E. Loizidou, F. Kaiser, A. J. Roecker, C. C. Dellios, X. W. Sun, G. Petrovic, *Angew. Chem.* **2005**, *117*, 3513 – 3518; *Angew. Chem. Int. Ed.* **2005**, *44*, 3447 – 3452; e) K. C. Nicolaou, P. K. Sasmal, A. J. Roecker, X. W. Sun, S. Mandal, A. Converso, *Angew. Chem.* **2005**, *117*, 3509 – 3513; *Angew. Chem. Int. Ed.* **2005**, *44*, 3443 – 3447.

[17] An interesting Ireland–Claisen rearrangement in the synthesis of saragossa acid C was published by Rizzacasa and co-workers: J. O. Bunte, A. N. Cuzzupe, A. M. Daly, M. A. Rizzacasa, *Angew. Chem.* **2006**, *118*, 6524 – 6528; *Angew. Chem. Int. Ed.* **2006**, *45*, 6376 – 6380.

[18] a) *The Claisen Rearrangement* (Eds.: M. Hiersemann, U. Nubbemeyer), Wiley-VCH, Weinheim, **2007**; b) A. M. Martin Castro, *Chem. Rev.* **2004**, *104*, 2939 – 3002.

[19] B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978 – 15979.