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Natural Product Synthesis

Total Synthesis of (±)-Platencin**

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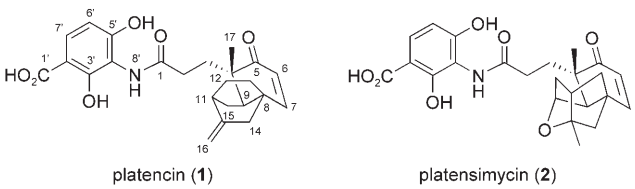
The discovery of penicillin represents a milestone in modern medicine.[1] Hailed as miracle drugs, penicillin and other antibiotics have helped millions of people around the world to fight off deadly infections and are credited with extending the average human life span by nearly ten years. These advances notwithstanding, the effectiveness of available antibiotics has diminished steadily as bacteria have evolved mechanisms to foil them.[2] Indeed, over the past decade there has been an alarming increase in infectious pathogens that are resistant to all commonly used antibiotics, even vancomycin, which until recently had been the drug of last resort. This growing prevalence of multidrug-resistant bacteria represents a major threat to human health and makes the identification and development of new classes of antibiotics imperative.[3]

In 2007, through mass screening of natural product extracts, scientists from Merck reported the identification of platencin (**1**),[4] a structurally novel antibacterial agent isolated from *Streptomyces platensis* MA7339 (Scheme 1). A

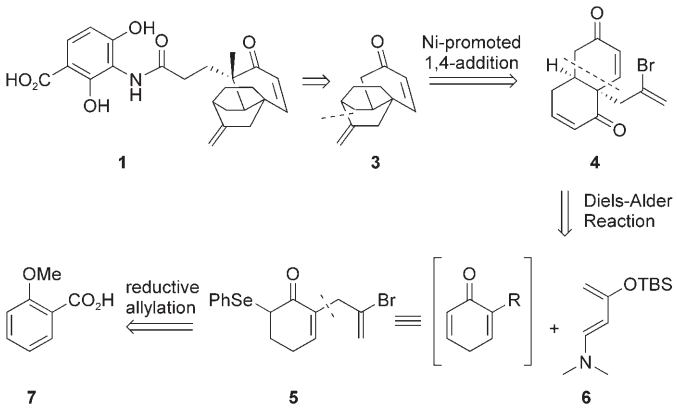


Scheme 1. Structures of platencin (**1**) and platensimycin (**2**).

year earlier, the same research group had reported the isolation of platensimycin (**2**)[5] from a different strain of the same bacteria. Both compounds display potent bactericidal activity against a broad spectrum of bacteria, including key antibiotic-resistant pathogens such as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, and *Streptococcus pneumoniae*. These compounds inhibit the biosynthesis of bacterial fatty acids through binding with the initiation condensing and elongation condensing enzymes FabH and FabF/B, respectively. Although the two natural products display similar activities, they have unique differences. For example, whereas platensimycin (**2**) primarily inhibits FabF, platencin (**1**) inhibits both FabF and FabH.[4] The targeting of two essential proteins rather than one should make it harder for bacteria to develop resistance to platencin (**1**).

The biological activity and unique structure of platensimycin (**2**) have sparked the interest of chemists around the world. An elegant total synthesis of the natural product was reported in the same year as the structure disclosure,[6a] and this was followed by nine other unique formal syntheses.[6,7] By contrast, there is little work reported towards the synthesis of platencin.[8] Herein we report an efficient total synthesis of (±)-platencin (**1**).

Platencin shares with platensimycin the polar 3-amino-2,4-dihydroxybenzoic acid unit, but differs in the intricacy of the lipophilic core. Whereas platensimycin possesses a bicyclo[3.2.1]octane carbon framework, platencin incorporates a bicyclo[2.2.2]octane skeleton. We envisioned formation of this core through a transition-metal-mediated intramolecular 1,4-conjugate addition reaction (Scheme 2), a



Scheme 2. Retrosynthetic analysis of platencin (**1**). TBS = *tert*-butyldimethylsilyl.

process that was also expected to install the requisite exo methylene unit. The bisenone-containing *cis*-decalin **4** was expected to come from the Diels–Alder reaction between diene **6** and an α-substituted cyclohexa-2,5-dienone—or its synthetic equivalent, compound **5**. Finally, enone **5** would be available through reductive allylation of *o*-anisic acid (**7**).

Scheme 3 provides an outline of the steps used to realize the above plan. The cyclohexadienone equivalent, selenide **5** was conveniently prepared from commercially available *o*-anisic acid (**7**). Birch reduction of **7** was followed by alkylation of the enolate intermediate with 2,3-dibromopropene.[9] The resulting allylated product was subjected to an acid work-up

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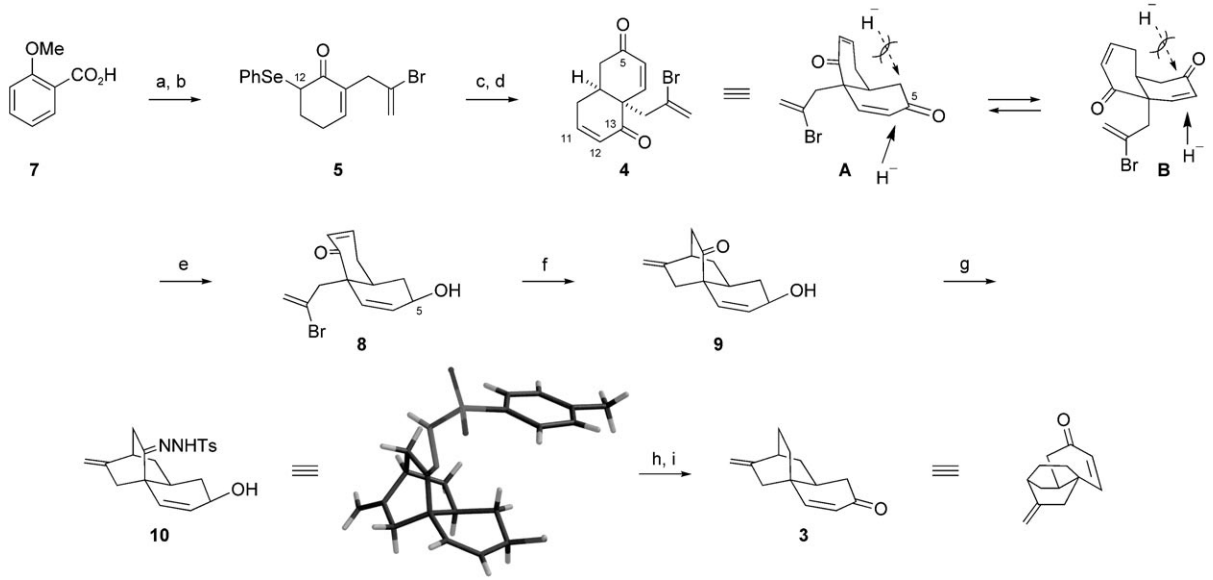
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 3. Synthesis of the platencin core (**3**). Reagents and conditions: a) Na, NH_3, 1,2-dibromoethane (1 mol%), 2,3-dibromopropene (1.25 equiv), −78 °C to 25 °C, then conc. HCl, 1,2-dichloroethane, reflux, 44%; b) LiHMDS (1.2 equiv), PhSeCl (1.3 equiv), THF, −78 °C, 83%; c) (*E*)-1-dimethylamino-3-*tert*-butyldimethylsiloxy-1,3-butadiene (**6**; 3.0 equiv), neat, 40 °C, then CH_2Cl_2, 49% aq HF, −78 °C to 25 °C, 72%; d) H_2O_2 (3.0 equiv), pyridine (2.0 equiv), CH_2Cl_2, 25 °C, 71%; e) DIBALH (1.5 equiv), THF, −78 °C, quant; f) $[Ni(cod)_2]$ (3.0 equiv), cod (6.0 equiv), MeCN, 25 °C, 69%; g) TsOH (10 mol%), $TsNHNH_2$ (1.2 equiv), THF, reflux, 98%; h) $NaBH_3CN$ (4.0 equiv), $ZnCl_2$ (1.0 equiv), EtOH, reflux, 92%; i) MnO_2 (10 equiv), CH_2Cl_2, 25 °C, 79%. cod = 1,5-cyclooctadiene, DIBALH = diisobutylaluminum hydride, HMDS = hexamethyldisilazane, Ts = *para*-toluenesulfonyl.

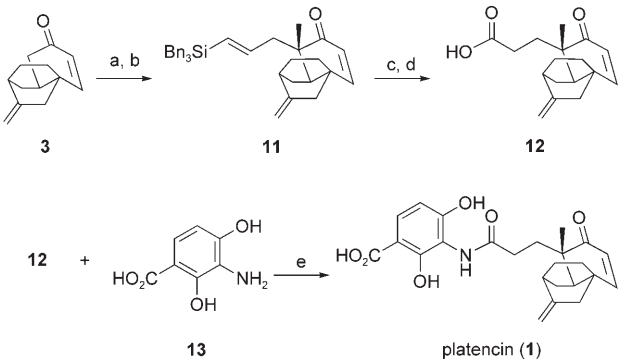
and heating, which accomplished hydrolysis of the enol ether and decarboxylation to cleanly afford the desired 2-(2-bromoallyl)-cyclohex-2-enone. Standard deprotonation/selenation provided enone **5** in 83% yield.

Construction of the *cis*-decalin, which contains a quaternary center, through a Diels–Alder reaction presents a significant challenge, as 2-alkyl-substituted cyclohexenones are reluctant participants in these reactions.[10] Diels–Alder reactions with such dienophiles require Lewis acid activation or high temperature, both of which can have a deleterious effect on highly electron-rich dienes. In this regard, we have developed the use of 1-amino-3-siloxybutadienes as alternate electron-rich dienes. We and others have shown such dienes to be highly reactive in uncatalyzed Diels–Alder and hetero-Diels–Alder reactions with a range of dienophiles.[11] Indeed, we were pleased to observe that the Diels–Alder reaction of enone **5** with aminosiloxy diene **6** proceeded well at 40 °C. Quenching the reaction at low temperature with 49% HF provided the requisite *cis*-decalin framework in 72% yield, as an inconsequential 1:1 mixture of selenophenyl diastereomers.[11i] Subsequent selenoxide formation/elimination afforded bisenone **4** in good yield.

Bisenone **4** is set up for construction of the central methylenebicyclo[2.2.2]octane unit, the identifying motif of platencin. Our plan was to use a $[Ni(cod)_2]$-promoted reductive cyclization reaction, a process similar to that developed by Delgado and co-workers.[12] These reactions typically involve the 5-*exo*-trig cyclization of a vinyl bromide precursor followed by β-hydride elimination of the nickel intermediate, or its capture by a suitable nucleophile. Interesting examples of this reaction which give 1,4-conjugate addition products have also been reported.[13] In the event, although the $[Ni(cod)_2]$-mediated cyclization of bisenone **4** was successful, it was low yielding. Examination of molecular models indicated that allylic alcohol **8** might be a better substrate for the cyclization, as it would exist preferentially in the chair-chair conformation, which is required for cyclization. The desired compound was obtained in quantitative yield and with complete regio- and stereoselectivity upon treatment of **4** with DIBALH at −78 °C. As expected, the less hindered carbonyl group was selectively reduced. The diastereofacial selectivity can be understood by considering the two chair-chair conformations (**A** and **B**) of the *cis*-decalin unit. In conformation **A**, axial hydride addition from the less hindered face would give the observed product. The same facial selectivity is expected for conformation **B**, although through equatorial attack.

Subjecting **8** to modified Delgado conditions—$[Ni(cod)_2]$ with added cod—promoted the desired reaction to provide tricyclic ketone **9** in good yield.[14] With the methylenebicyclo-[2.2.2]octane skeleton secured, what remained were adjustments to the oxidation states. In preparation for the ketone deoxygenation, compound **9** was converted into tosylhydrazone **10**, which was obtained as a crystalline solid in 98% yield. The X-ray analysis for this compound confirmed the bicyclo[2.2.2]octane connectivity assigned to the cyclization product. Subjecting **10** to the protocol developed by Caglioti and Magi,[15] using $NaBH_3CN$ in the presence of $ZnCl_2$, provided the saturated product. Finally, the allylic alcohol was smoothly oxidized with MnO_2 to afford the platencin core **3** in 79% yield.

With the core of platencin completed, the final challenges included diastereoselective introduction of the methyl and propionate groups as well as the coupling of the resulting carboxylic acid with 3-amino-2,4-dihydroxybenzoic acid (Scheme 4). This very same functionality is present in



Scheme 4. Completion of the synthesis of platencin (**1**). Reagents and conditions: a) KHMDS (1.5 equiv), MeI (8.0 equiv), THF/HMPA, −78 °C, 87%; b) (*E*)-1-tribenzylsilyl-3-iodo-prop-1-ene (1.5 equiv), KHMDS (1.3 equiv), THF/HMPA, −78 °C, 73%; c) TBAF (5.0 equiv), iodosobenzene (1.2 equiv), H_2O_2 (6.0 equiv), $KHCO_3$ (5.0 equiv), THF, 0 to 40 °C, 89%; d) $NaClO_2$ (10 equiv), NaH_2PO_4 (15 equiv), 2,3-dimethylbutene (30 equiv), *t*BuOH/H_2O, quant; e) **13** (2.0 equiv), DCC (1.3 equiv), DMAP (2.0 equiv) Et_3N (3.0 equiv), MeCN/DMF, RT, 62%. Bn = benzyl, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosphoramide, TBAF = tetra-*n*-butylammonium fluoride.

platensimycin and its introduction had already been addressed through a seven-step sequence in the landmark synthesis of this natural product by Nicolaou et al.[6a] Our route to the endgame is shown in Scheme 4 and takes advantage of the diastereoselective double-alkylation process. In an effort to access the propionic acid unit more directly, the allylation was carried out using (*E*)-1-tribenzylsilyl-3-iodo-prop-1-ene[16] to give the desired product **11** in good yield and with complete diastereoselectivity. However, the Tamao oxidation[17] of the vinyl silane proved difficult and was complicated by the competing epoxidation of the enone moiety. We discovered that the oxidation proceeded cleanly when an equivalent of iodosobenzene was added to the reaction.[18] This new oxidation protocol provided the desired aldehyde product in excellent yield (89%). Subsequent Lindgren–Kraus oxidation[19] afforded the desired carboxylic acid **12** in quantitative yield.

In the syntheses of platensimycin and platencin, fully or partially protected anilines (for example **13**)[20] were coupled to the core carboxylic acids.[6a,8] We reasoned that the direct coupling of the fully unprotected aniline with the acid would be feasible. Even if the initial coupling product was either an anhydride or one of the two possible phenolic esters then, based on thermodynamic considerations, the intermediate was expected to transfer in an intramolecular fashion into the desired amide product. As expected, treatment of carboxylic acid **12** with DCC, DMAP, and Et_3N followed by the addition of aniline **13** afforded platencin (**1**) in 62% yield.

In summary, we have developed a concise and stereocontrolled route to platencin. The synthesis features: 1) a challenging Diels–Alder reaction with an α substituted cyclohexenone, 2) a [Ni(cod)$_2$]-promoted cyclization reaction to generate the bicyclo[2.2.2]octane framework, 3) a novel protocol for the Tamao oxidation, and 4) a direct, protecting group free coupling strategy for introduction of the anilide unit. This strategy not only lends itself to the asymmetric synthesis but also to the preparation of diverse analogues of this important antibiotic lead compound.

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[1] M. Friedman, G. W. Friedland, *Medicine's Ten Greatest Discoveries*, Yale University Press, New Heaven, CT, **1998**, pp. 263.
[2] a) C. Walsh, *Antibiotics: Actions, Origin, Resistance*, ASM Press, Washington, DC, **2003**; b) S. B. Singh, J. F. Barrett, *Biochem. Pharmacol.* **2006**, *71*, 1006–1015.
[3] a) C. Walsh, *Nat. Rev. Microbiol.* **2003**, *1*, 65–70; b) C. H. T. Wright, K. A. Reynolds, *Curr. Opin. Microbiol.* **2007**, *10*, 447–453.
[4] a) H. Jayasuriya, K. B. Herath, C. Zhang, D. L. Zink, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, I. Gonzalez, O. Salazar, F. Pelaez, R. Cummings, S. Ha, J. Wang, S. B. Singh, *Angew. Chem.* **2007**, *119*, 4768–4772; *Angew. Chem. Int. Ed.* **2007**, *46*, 4684–4688; b) J. Wang, S. Kodali, S. H. Lee, A. Galgoci, R. Painter, K. Dorso, F. Racine, M. Motyl, L. Hernandez, E. Tinney, S. L. Colletti, K. Herath, R. Cummings, O. Salazar, I. Gonzalez, A. Basilio, F. Vicente, O. Genilloud, F. Pelaez, H. Jayasuriya, K. Young, D. F. Cully, S. B. Singh, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 7612–7616.
[5] a) J. Wang, S. M. Soisson, K. Young, W. Shoop, S. Kodali, A. Galgoci, R. Painter, G. Parthasarathy, Y. S. Tang, R. Cummings, S. Ha, K. Dorso, M. Motyl, H. Jayasuriya, J. Ondeyka, K. Herath, C. Zhang, L. Hernandez, J. Allocco, A. Basilio, J. R. Tormo, O. Genilloud, F. Vicente, F. Pelaez, L. Colwell, S. H. Lee, B. Michael, T. Felcetto, C. Gill, L. L. Silver, J. D. Hermes, K. Bartizal, J. Barrett, D. Schmatz, J. W. Becker, D. Cully, S. B. Singh, *Nature* **2006**, *441*, 358–361; b) S. B. Singh, H. Jayasuriya, J. G. Ondeyka, K. B. Herath, C. Zhang, D. L. Zink, N. N. Tsou, R. G. Ball, A. Basilio, O. Genilloud, M. T. Diez, F. Vicente, F. Pelaez, K. Young, J. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 11916–11920; c) S. B. Singh, K. B. Herath, J. Wang, N. Tsou, R. G. Ball, *Tetrahedron Lett.* **2007**, *48*, 5429–5433; d) K. B. Herath, A. B. Attygalle, S. B. Singh, *J. Am. Chem. Soc.* **2007**, *129*, 15422–15423.
[6] a) K. C. Nicolaou, A. Li, D. J. Edmonds, *Angew. Chem.* **2006**, *118*, 7244–7248; *Angew. Chem. Int. Ed.* **2006**, *45*, 7086–7090; b) K. C. Nicolaou, Y. Tang, J. Wang, *Chem. Commun.* **2007**, 1922–1923; c) K. C. Nicolaou, D. J. Edmonds, A. Li, G. S. Tria, *Angew. Chem.* **2007**, *119*, 4016–4019; *Angew. Chem. Int. Ed.* **2007**, *46*, 3942–3945; d) Y. Zou, C. Chen, C. D. Taylor, B. M. Foxman, B. B. Snider, *Org. Lett.* **2007**, *9*, 1825–1828; e) K. P. Kaliappan, V. Ravikumar, *Org. Lett.* **2007**, *9*, 2417–2419; f) P. Li, J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 9534–9535; g) K. Tiefenbacher, J. Mulzer *Angew. Chem.* **2007**, *119, 8220–8221; Angew. Chem. Int. Ed.* **2007**, 46, 8074–8075; *Angew. Chem. Int. Ed.* **2007**, *46*, 8074–8075; h) A. K. Ghosh, K. Xi, *Org. Lett.* **2007**, *9*, 4013–4016; i) G. Lalic, E. J. Corey, *Org. Lett.* **2007**, *9*, 4921–4923; j) P. Heretsch, A. Giannis, *Synthesis* **2007**, 2614–

2616; k) K. C. Nicolaou, D. Pappo, K. Y. Tsang, R. Gibe, D. Y. Chen, *Angew. Chem.* **2008**, *120*, 958 – 960; *Angew. Chem. Int. Ed.* **2008**, *47*, 944 – 946; l) K. Tiefenbacher, J. Mulzer, *Angew. Chem.* **2008**, *120*, 2582 – 2590; *Angew. Chem. Int. Ed.* **2008**, *47*, 2548 – 2555.

[7] Studies on synthetic analogues of platensimycin: a) K. C. Nicolaou, T. Lister, R. M. Denton, A. Montero, D. J. Edmonds, *Angew. Chem.* **2007**, *119*, 4796 – 4798; *Angew. Chem. Int. Ed.* **2007**, *46*, 4712 – 4714; b) K. C. Nicolaou, Y. Tang, J. Wang, A. F. Stepan, A. Li, A. Montero, *J. Am. Chem. Soc.* **2007**, *129*, 14850 – 14851.

[8] As this manuscript was being prepared for submission, the first total synthesis of platencin was reported: K. C. Nicolaou, G. S. Tria, D. J. Edmonds, *Angew. Chem.* **2008**, *120*, 1804 – 1807; *Angew. Chem. Int. Ed.* **2008**, *47*, 1780 – 1783.

[9] a) D. F. Taber, *J. Org. Chem.* **1976**, *41*, 2649 – 2650; b) D. F. Taber, B. P. Gunn, I.-C. Chiu, *Org. Synth.* **1983**, *61*, 59 – 61.

[10] a) S. Danishefsky, T. Kitahara, C. F. Yan, J. Morris, *J. Am. Chem. Soc.* **1979**, *101*, 6996 – 7000; b) F. Fringuelli, F. Pizzo, A. Taticchi, E. Wenkert, *J. Org. Chem.* **1983**, *48*, 2802 – 2808; c) M. Ge, B. M. Stoltz, E. J. Corey, *Org. Lett.* **2000**, *2*, 1927 – 1929; d) A. Gagnon, S. J. Danishefsky, *Angew. Chem.* **2002**, *114*, 1651 – 1654; *Angew. Chem. Int. Ed.* **2002**, *41*, 1581 – 1584; e) M. E. Jung, D. Ho, H. V. Chu, *Org. Lett.* **2005**, *7*, 1649 – 1651; f) S.-J. Min, G. O. Jones, K. N. Houk, S. J. Danishefsky, *J. Am. Chem. Soc.* **2007**, *129*, 10078 – 10079.

[11] a) S. A. Kozmin, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 5252 – 5253; b) S. A. Kozmin, J. M. Janey, V. H. Rawal, *J. Org. Chem.* **1999**, *64*, 3039 – 3052; c) S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **1999**, *121*, 9562 – 9573; d) J. Renaud, C. Aubert, M. Malacria, *Tetrahedron Lett.* **1999**, *40*, 5015 – 5018; e) P. P. Seth, N. I. Totah, *Org. Lett.* **1999**, *1*, 1411 – 1414; f) R. Paczkowski, C. Maichle-Mossmer, M. E. Maier, *Org. Lett.* **2000**, *2*, 3967 – 3969; g) T. L. S. Kishbaugh, G. W. Gribble, *Tetrahedron Lett.* **2001**, *42*, 4783 – 4785; h) Y. Huang, V. H. Rawal, *J. Am. Chem. Soc.* **2002**, *124*, 9662 – 9663; i) Y. Huang, V. H. Rawal, *Org. Lett.* **2000**, *2*, 3321 – 3323; j) R. Kawęcki, *Tetrahedron: Asymmetry* **2006**, *17*, 1420 – 1423; k) A. B. Smith, K. Basu, T. Bosanac, *J. Am. Chem. Soc.* **2007**, *129*, 14872 – 14874.

[12] a) D. Sole, Y. Cancho, A. Llebaria, J. M. Moreto, A. Delgado, *J. Am. Chem. Soc.* **1994**, *116*, 12133 – 12134; b) D. Sole, J. Bonjoch, J. Bosch, *J. Org. Chem.* **1996**, *61*, 4194 – 4195.

[13] a) D. Sole, J. Bonjoch, J. Bosch, *J. Org. Chem.* **1996**, *61*, 4194 – 4195; 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.

[14] The cod was added to make up for any that might escape during the reaction and thereby prevent degradation of the highly reactive nickel species during the reaction.

[15] L. Caglioti, M. Magi, *Tetrahedron* **1963**, *19*, 1127 – 1131.

[16] (*E*)-1-Tribenzylsilyl-3-iodo-prop-1-ene was prepared from propargyl alcohol in two steps, see the Supporting Information.

[17] a) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694 – 1696; b) K. Tamao, M. Kumada, K. Maeda, *Tetrahedron Lett.* **1984**, *25*, 321 – 324; c) I. Fleming, R. Henning, H. Plaut, *J. Chem. Soc. Chem. Commun.* **1984**, 29 – 31.

[18] The role of iodosobenzene in this reaction is under investigation, and the details will be reported in due course.

[19] The chlorite oxidation of aldehydes has been referred to in the literature as the Pinnick oxidation. However, in his report on the oxidation of α,β-unsaturated aldehydes, Professor Pinnick credits Lindgren and Kraus for the key developments of this reaction; see: a) B. O. Lindgren, T. Nilsson, *Acta Chem. Scand.* **1973**, *27*, 888 – 890; b) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175 – 1176; c) G. A. Kraus, B. Roth, *J. Org. Chem.* **1980**, *45*, 4825 – 4830; d) B. S. Bal, W. E. Childers, H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091 – 2096.

[20] 3-Amino-2,4-dihydroxybenzoic acid **13** was prepared from 2,4-dihydroxybenzoic acid in four steps, see the Supporting Information.

