Asymmetric Synthesis

Deutsche Ausgabe: DOI: 10.1002/ange.201501143
Internationale Ausgabe: DOI: 10.1002/anie.201501143

Stereoselective Synthesis of the Halaven C14–C26 Fragment from D-Quinic Acid: Crystallization-Induced Diastereoselective Transformation of an α-Methyl Nitrile**

Francis Belanger, Charles E. Chase, Atsushi Endo, Francis G. Fang, Jing Li, Steven R. Mathieu, Annie Z. Wilcoxen, and Huiming Zhang*

Abstract: *Crystallization-induced diastereoselective transformation (CIDT) of an α-methyl nitrile completes an entirely non-chromatographic synthesis of the halichondrin B C14–C26 stereochemical array. The requisite α-methyl nitrile substrate is derived from D-quinic acid through a series of substrate-controlled stereoselective reactions via a number of crystalline intermediates that benefit from a rigid polycyclic template. Therefore, all four stereogenic centers in the Halaven C14–C26 fragment were derived from the single chiral source D-quinic acid.*

The important role of total synthesis in the discovery and development of novel medicines was highlighted by the recent approval of Halaven (**1**),[1] a fully synthetic analogue of the marine natural product halichondrin B (**2**),[2,3] for treatment of certain patients with advanced breast cancer (Figure 1). A characteristic feature of the manufacturing process for two of the three fragments (C1–C13 and C27–C35) was the employment of stereocontrol on cyclic carbohydrate templates to enable the discovery of crystallization-based routes.[4] The third fragment **3** (C14–C26), although not the most structurally complex, presents a distinct challenge within the overall synthesis owing to the presence of multiple non-contiguous acyclic stereogenic centers.[5] Reconfiguration of **3** as cyclic iodoether **4** could provide a conceptually different approach to **3** wherein the acyclic stereogenic centers are established on a bicyclic template.[6] It was hoped that a rigid template would impart a high degree of innate crystallinity to the intermediates, thereby allowing crystallization, rather than chromatography, to be the key quality control technology. Proof of concept on the viability of a bicyclic iodoether template as a synthetic precursor was quickly demonstrated by stereoselective iodoetherification of **3** to provide **4** and zinc-mediated reductive elimination of **4** to regenerate **3**. Whereas the *cis*-fused bicyclic template in **4** clearly suggests methods to relate the configurations at the C17, C20, and C23 positions, establishment of the fourth ancillary stereogenic center (C25) would require an acyclic stereocontrol strategy. Furthermore, a convenient chiral origin for the bicyclic system would need to be identified. Herein, we report the successful realization of these goals and: 1) the use of D-quinic acid as a readily available chiral source for all of the stereogenic centers in **3**, 2) the first example of a crystallization-induced diastereoselective trans-

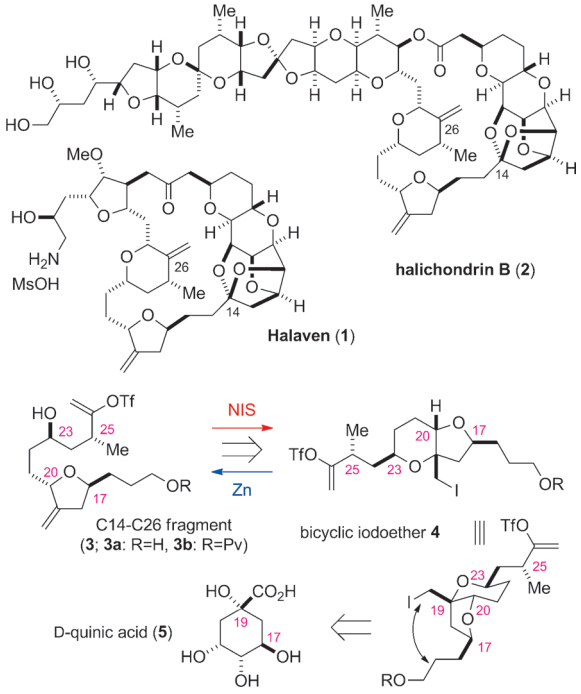


Figure 1. Synthesis strategy towards the Halaven C14–C26 fragment. Ms = methanesulfonyl, NIS = *N*-iodosuccinimide, Pv = pivaloyl, Tf = trifluoromethanesulfonyl.

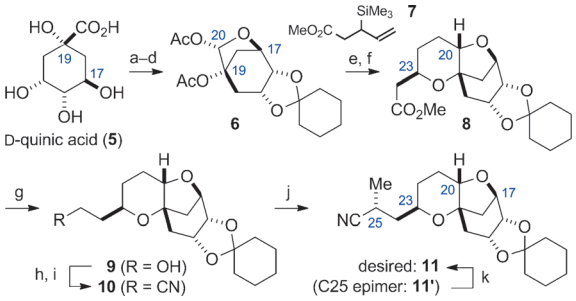
[*] Dr. C. E. Chase, Dr. A. Endo, Dr. F. G. Fang, Dr. J. Li, S. R. Mathieu
Next Generation Systems
Eisai Inc. 4 Corporate Drive, Andover, MA 01810 (USA)
E-mail: Frank_Fang@eisai.com
F. Belanger
Current address: PCAS BioMatrix, 725 Trotter St., Saint-Jean-sur-Richelieu, Quebec J3B 8 J8 (Canada)
Dr. A. Z. Wilcoxen
Current address: Amgen
One Kendall Square, 360 Binney St. Cambridge, MA 02142 (USA)
H. Zhang
Current address: Johnson Matthey Pharma Services
75 Patton Rd. Devens, MA 01434 (USA)

[**] We thank our analytical chemistry colleagues Jian Del Vecchio, Thomas Noland, Kristen Lacasse, and Noritsugu Maki for HPLC method development, process research colleagues Robert Giusto and William Powazinik for calorimetry, and the chemical development department for pilot plant production. We thank Dr. Richard Staples (Crystallographic Resources, Inc.) for X-ray structural analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201501143.

formation[7] of an α-methyl nitrile, and 3) crystallization-based stereochemical quality control benefiting from a rigid bridged polycyclic system.

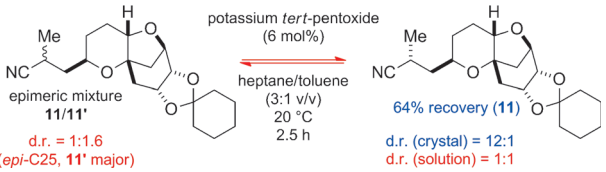
D-Quinic acid (**5**) was transformed into the crystalline diacetate **6** by lactonization,[8] partial reduction, and peracetylation (Scheme 1). Lewis acid mediated C glycosidation of **6** with commercially available 3-trimethylsilyl-methyl-4-pentenoate (**7**),[3a,9] followed by sodium methoxide treatment, stereoselectively established the C20 (single isomer) and C23 (9:1 d.r.) stereogenic centers of polycyclic pyran **8**. Ester **8** was homologated to nitrile **10** by reduction (step g, **8**→**9**), activation (step h), and cyanide displacement (step i). Crystallization of **10** enhanced the C23 stereochemical quality to >100:1. Therefore, a crystalline intermediate has been rapidly assembled with essentially complete control of three of the four stereogenic centers (C17, C20, and C23) of **3**.



Scheme 1. Synthesis of α-methyl nitrile **11** from D-quinic acid (**5**). Reagents and conditions: a) cyclohexanone, *p*-TsOH·H_2O, toluene, reflux, 95%; b) TMSCl, imidazole, toluene, 20°C; c) DIBAL, toluene, −78°C; d) 1) AcOH, H_2O, DMAP, THF, 20°C, 2) Ac_2O, NEt_3, 20°C, 72% (3 steps); e) **7**, BF_3·OEt_2, Tf_2O, CH_3CN, 20°C; f) NaOMe, THF/MeOH, 10°C; g) $LiAlH_4$, THF, 15°C; h) MsCl, NEt_3, THF, 25°C; i) KCN, EtOH/H_2O, 70°C, 30% from **6**; j) 1) KHMDS (1.1 equiv), MeI, toluene/THF, −75°C, 2) KHMDS (0.15 equiv), −75°C; k) KHMDS (0.60 equiv), toluene, −70°C (recycling of filtrates), 72% from **10**. Steps a, d, f, h, i, and j/k gave crystalline products. DIBAL = diisobutylaluminum hydride, DMAP = 4-dimethylaminopyridine, KHMDS = potassium hexamethyldisilazane, *p*-TsOH = *para*-toluenesulfonic acid, TMS = trimethylsilyl.

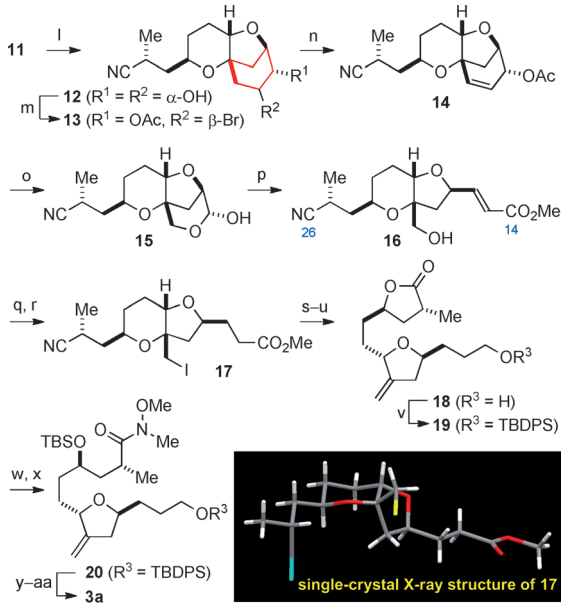
LDA treatment of **10** followed by quenching with methyl iodide afforded a 1:1 mixture of α-methyl nitrile **11** (m.p. 123°C) and the C25 epimer **11′** (m.p. 82°C). Fortuitously, the desired isomer **11** exhibited greater crystallinity. Mindful of the results of Fleming et al.,[10] KHMDS was investigated as an alternative base in the hope that a larger counterion would enhance chelation to the pyran oxygen atom. Encouragingly, the selectivity improved to 2:1 (step j, part 1). Moreover, in situ treatment with a catalytic amount of the base enhanced the selectivity to >4:1. Crystallization of the crude mixture provided **11** with a diastereomeric ratio of 20:1–30:1 at the C25 carbon atom (step j, part 2). The filtrates (1:2 d.r., **11′** as the major diastereomer) were re-equilibrated and crystallized to provide additional **11** (step k).

The results suggested the possibility of a crystallization-induced diastereoselective transformation as a method to control the C25 stereogenic center. In the event, treatment of the epimeric mixture (**11**/**11′**, d.r. = 1:1.6, **11′** as the major diastereomer) with a catalytic amount of potassium *tert*-pentoxide equilibrated and precipitated **11** with 12:1 d.r. (Scheme 2).



Scheme 2. Crystallization-induced diastereoselective transformation.

With all four stereogenic centers, C17, C20, C23, and C25, firmly established, unraveling the quinic acid cyclohexane ring (highlighted in red) was accomplished as depicted in Scheme 3. Cyclohexylidene cleavage (step l, **11**→**12**), regioselective bromoacetate formation[11] (step m, **12**→**13**), and dehydrobromination (step n) afforded crystalline allylic acetate **14**. Ozonolysis of **14** (step o, part 1), borohydride quench (step o, part 2), deacetylation (step o, part 3), and periodate cleavage (step o, part 4) provided crystalline lactol **15** from a single-pot sequence.



Scheme 3. Reagents and conditions: l) PhNH−NH_2·HCl, TsOH·H_2O, MeOH, 55°C, 99%; m) BrC(=O)CMe_2(OAc), CH_3CN, cat. H_2O, 0°C; n) DBU, toluene, 100°C, 47% (2 steps); o) 1) O_3, isopropyl acetate/MeOH, −30°C, 2) $NaBH_4$, −20°C, 3) K_2CO_3, RT, 4) $NaIO_4$, THF/H_2O, RT, 90%; p) $(MeO)_2POCH_2CO_2Me$, $(iPr)_2NEt$, LiCl, CH_3CN, 18°C, 98%; q) H_2, Pd/C, $(iPr)_2NEt$, EtOAc, RT, 89%; r) 1) Tf_2O, 2,6-lutidine, MTBE, 0°C, 2) NaI, DMF, RT, 81%; s) $LiBH_4$, MeOH, THF/toluene, 13°C; t) Zn, AcOH, THF/H_2O, 0°C, 99% (2 steps); u) 1) HCl, 2-PrOH/toluene, 25°C, 2) H_2O, 45°C, 94%; v) TBDPSCl, imidazole, DMF, 23°C; w) HNMe(OMe)·HCl, Me_3Al, CH_2Cl_2/toluene, 0°C; x) TBSCl, imidazole, DMF, 23°C; y) MeMgCl, THF, 0°C; z) Tf_2NPh, KHMDS, THF/toluene, −20°C; aa) HCl, 2-PrOH/MeOH, RT, 49% from **18**. Steps l, m, n, o, and r gave crystalline products. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBDPS = *tert*-butyldiphenylsilyl, TBS = *tert*-butyldimethylsilyl.

Horner–Wadsworth–Emmons reaction of **15** under Roush–Masamune conditions[12] afforded the α,β-unsaturated ester **16** (step p). Catalytic hydrogenation (step q) followed by triflate-mediated iodination of the neopentyl alcohol (step r, presumably assisted by the neighboring pyran oxygen atom) afforded iodoester **17** as a crystalline solid, wherein all stereogenic centers (C17, C20, C23, and C25) were controlled to d.r. > 1000:1. Reduction of iodoester **17** with $LiBH_4$ (step s), followed by a zinc-mediated Vasella fragmentation (step t),[13] proceeded smoothly under mild conditions to furnish the C19 exocyclic olefin while liberating the C23 hydroxy group. Anhydrous HCl treatment to form a cyclic imidate hydrochloride followed by hydrolytic lactonization provided **18** (step u). Lactone **18** was converted into known Weinreb amide **20**[4d] by a sequence consisting of protection of the C14 free alcohol (step v), lactone opening to give the Weinreb amide (step w), and protection of the C23 hydroxy functional group (step x). The previously described three-step process (steps y–aa)[4d] provides the C14–C26 fragment **3a** with a quality suitable for downstream processing.

A comparison of the operational efficiency of the previous, more convergent manufacturing process (20 total steps, 1% overall yield for the longest linear sequence of 13 steps)[4d] versus the new route towards the C14–C26 fragment (27 steps, 2% overall yield) is provided in Figure 2, specifically highlighting raw-material cost and waste minimization (aspects of "green chemistry"). A 78% cost improvement and 80% waste reduction were achieved primarily by eliminating the vast quantities of solvents required for extensive chromatographic purification. Moreover, stereochemical quality control at all four stereogenic centers was significantly facilitated by relying on crystallization rather than chromatography for purification.

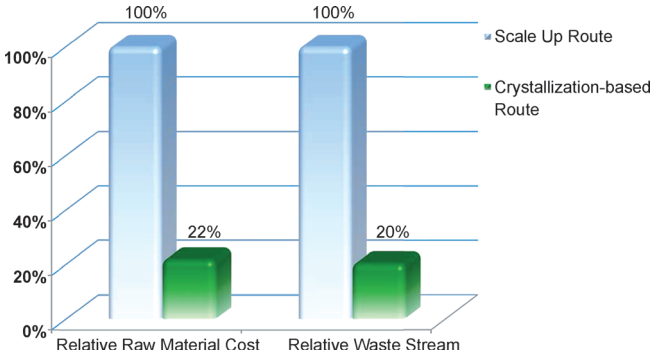


Figure 2. Impact of the crystallization-based synthesis of the C14–C26 fragment on raw material cost and waste reduction.

In conclusion, a new synthesis of the halichondrin/Halaven C14–C26 fragment **3a** has been established, which features a number of substrate-controlled transformations starting from readily available D-quinic acid (**5**) as the single source of chirality. A novel feature of the overall route, the stereoselective formation of α-methyl nitrile **11** in a crystallization-induced diastereoselective transformation, served as a cornerstone for crystallization-based quality control for the entire sequence. A perhaps underappreciated aspect of translating a natural product synthesis to a practical manufacturing process is the importance of crystallization in the design strategy. A classical cyclic stereocontrol approach, although sometimes lengthier, often benefits from a great number of crystalline intermediates.

Keywords: antitumor agents · asymmetric synthesis · chiral pool · green chemistry · total synthesis

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 5108–5111
Angew. Chem. **2015**, *127*, 5197–5200

[1] For the discovery and development of **1**, see: a) B. A. Littlefield, M. H. Palme, B. M. Seletsky, M. J. Towle, M. J. Yu, W. Zheng, World Patent, 9965894, **1999**; b) M. J. Towle et al., *Cancer Res.* **2001**, *61*, 1013; c) W. Zheng et al., *J. Bioorg. Med. Chem. Lett.* **2004**, *14*, 5551; d) M. J. Yu, Y. Kishi, B. A. Littlefield in *Anticancer Agents from Natural Products*, 1st ed. (Eds.: G. M. Cragg, D. G. I. Kingston, D. J. Newman), Taylor & Francis Group CRC Press, Boca Raton, FL, **2005**, pp. 241–265; e) L. T. Vahdat, B. Pruitt, C. J. Fabian, R. R. Rivera, D. A. Smith, E. Tan-Chiu, J. Wright, A. R. Tan, N. A. DaCosta, E. Chuang, J. Smith, J. O'Shaughnessy, D. E. Shuster, N. L. Meneses, K. Chandrawansa, F. Fang, P. E. Cole, S. Ashworth, J. L. Blum, *J. Clin. Oncol.* **2009**, *27*, 2954; f) M. J. Yu, Y. Kishi, B. A. Littlefield in *Anticancer Agents from Natural Products*, 2nd ed. (Eds.: G. M. Cragg, D. G. I. Kingston, D. J. Newman), Taylor & Francis Group CRC Press, Boca Raton, FL, **2012**, pp. 317–345; g) P. A. Kaufman, A. Awada, C. Twelves, L. Yelle, E. A. Perez, G. Velikova, M. S. Olivo, Y. He, C. E. Dutcus, J. Cortes, *J. Clin. Oncol.* **2015**, *33*, 594.

[2] For the discovery of the halichondrins, see: a) D. Uemura, K. Takahashi, T. Yamamoto, C. Katayama, J. Tanaka, Y, Okumura, Y. Hirata, *J. Am. Chem. Soc.* **1985**, *107*, 4796; b) Y. Hirata, D. Uemura, *Pure Appl. Chem.* **1986**, *58*, 701.

[3] For the total synthesis of **2**, see: a) T. D. Aicher, K. R. Buszek, F. G. Fang, C. J. Forsyth, S. H. Jung, Y. Kishi, M. C. Matelich, P. M. Scola, D. M. Spero, S. K. Yoon, *J. Am. Chem. Soc.* **1992**, *114*, 3162; for the total synthesis of norhalichondrin B, see: b) K. L. Jackson, J. A. Henderson, H. Motoyoshi, A. J. Phillips, *Angew. Chem. Int. Ed.* **2009**, *48*, 2346; *Angew. Chem.* **2009**, *121*, 2382; for the total synthesis of halichondrin C, see: c) A. Yamamoto, A. Ueda, P. Brémond, P. S. Tiseni, Y. Kishi, *J. Am. Chem. Soc.* **2012**, *134*, 893; for a review on the synthetic work towards the halichondrins, see: d) K. L. Jackson, J. A. Henderson, A. J. Phillips, *Chem. Rev.* **2009**, *109*, 3044, and references therein.

[4] a) B. Austad, C. E. Chase, F. G. Fang, World Patent, 118565, **2005**; b) H. Chiba, K. Tagami, *J. Synth. Org. Chem. Jpn.* **2011**, *69*, 600; for the synthesis of the C1–C13 fragment, see: c) C. E. Chase, F. G. Fang, B. M. Lewis, M. J. Schnaderbeck, G. D. Wilkie, X. Zhu, *Synlett* **2013**, 323; for the synthesis of the C27–C35/C14–C35 fragments, see: d) B. C. Austad et al., *Synlett* **2013**, 327; for the assembly of **1**, see: e) B. C. Austad et al., *Synlett* **2013**, 333.

[5] For new syntheses of the Halaven C14–C35 fragment and the halichondrin C14–C38 fragment, see: a) D.-S. Kim, C. G. Dong, J. T. Kim, H. Guo, J. Huang, P. S. Tiseni, Y. Kishi, *J. Am. Chem. Soc.* **2009**, *131*, 15636; b) C. G. Dong, J. A. Henderson, Y. Kaburagi, T. Sasaki, D. S. Kim, J. T. Kim, D. Urabe, H. Guo, Y. Kishi, *J. Am. Chem. Soc.* **2009**, *131*, 15642.

[6] For the use of cyclic haloethers for stereoselective synthesis, see: a) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, R. W. Kierstead, *J. Am. Chem. Soc.* **1956**, *78*, 2023; b) E. J. Corey, R. Noyori, *Tetrahedron Lett.* **1970**, *11*, 311.

[7] N. G. Anderson, *Org. Process Res. Dev.* **2005**, *9*, 800.

[8] G. Ulibarri, W. Nadler, T. Skrydstrup, H. Audrain, A. Chiaroni, C. Riche, D. S. Grierson, *J. Org. Chem.* **1995**, *60*, 2753 – 2761.
[9] D. P. Stamos, Y. Kishi, *Tetrahedron Lett.* **1996**, *37*, 8643.
[10] F. F. Fleming, B. C. Shook, *Tetrahedron* **2002**, *58*, 1.
[11] a) A. R. Mattocks, *J. Chem. Soc.* **1964**, 1918; b) A. R. Mattocks, *J. Chem. Soc.* **1964**, 4840.
[12] M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183.
[13] B. Bernet, A. Vasella, *Helv. Chim. Acta* **1979**, *62*, 1990.

Received: February 5, 2015
Published online: March 30, 2015