Communications

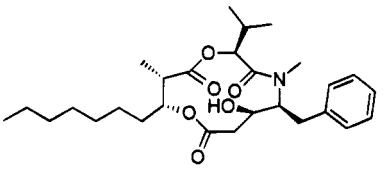
A Convergent Total Synthesis of the Multidrug Resistance-Reversing Agent Hapalosin

Tam Q. Dinh and Robert W. Armstrong*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095

Received September 26, 1995

Cytotoxic drugs often fail to kill tumor cells long-term because overexpression or activation of transmembrane P-glycoproteins results in efflux of the drugs.[1] Compounds that can contravene P-glycoprotein-mediated multidrug resistance (MDR) and, hence, increase intracellular drug concentration may be useful in chemotherapy. The novel cyclic depsipeptide hapalosin (**1**) was recently isolated and has shown auspicious anti-MDR activity *in vitro*.[2] The first total synthesis of hapalosin has been accomplished.



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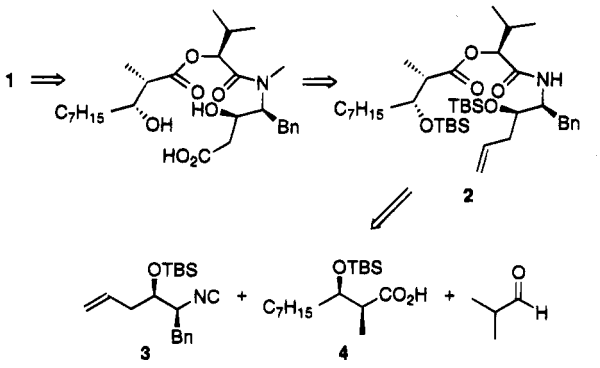
The synthesis of hapalosin was initially envisioned to incorporate a Passerini reaction[3] (Scheme 1). Since the Passerini reaction is a multiple-component condensation, it permits the ready utilization of different aldehydes or ketones to create analogs of hapalosin. Passerini reactions of isocyanide **3**, acid **4**, and isobutyraldehyde at room temperature produced the two separable diastereomers of olefin **2** in about 66% yield, but the diastereoselectivity (ds) was poor. Attempts to improve the ds by using various solvents were unsuccessful as the undesired diastereomer was slightly favored in all reactions. More important, clean N-methylation of olefin **2** or related structures without an α-H in the acid component could not be achieved, prompting consideration of another strategy.

Hapalosin was synthesized by another route which utilized the acid chloride coupling method to form an intermediate similar to **2** (Scheme 2). The synthesis converged at fragments **6** and **7**. Brown allylboration of an aldehyde derivative of L-Phe led to amino alcohol **6**. Another Brown allylboration of octanal set the two contiguous stereocenters in acid **7**. A third key step was the macrolactonization of hydroxyacid **5**.

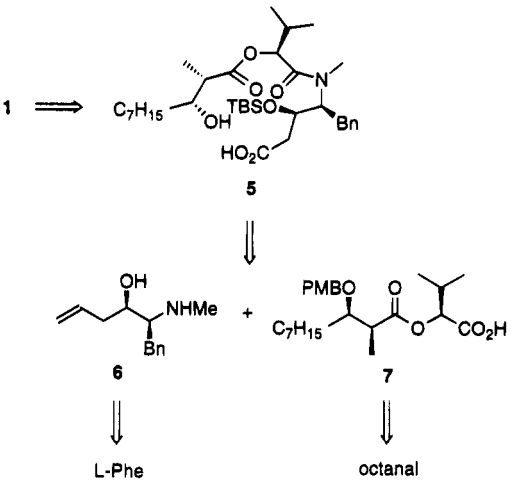
Amino alcohol **6** was synthesized in four steps starting with *N*-BOC-L-Phe methyl ester **8** (Scheme 3). The amino ester was *N*-methylated with NaH and MeI[4] (97% yield) and reduced to the aldehyde with DIBAH (60% yield).[5] Aldehyde **9** underwent Brown allylboration[6] to give the desired diastereomer **10** in 64% yield and 90% de, the de being determined at the stage of amino alcohol **6**. All *N*,*N*-dialkylamides and -carbamates in Schemes 3 and 5 exist as rotamers in $CDCl_3$ at room temperature. This characteristic renders very complicated the interpretation of ^{1}HMR spectra acquired at room temperature of compounds more advanced than **9**.

Synthesis of the second fragment, ester acid **7**, is

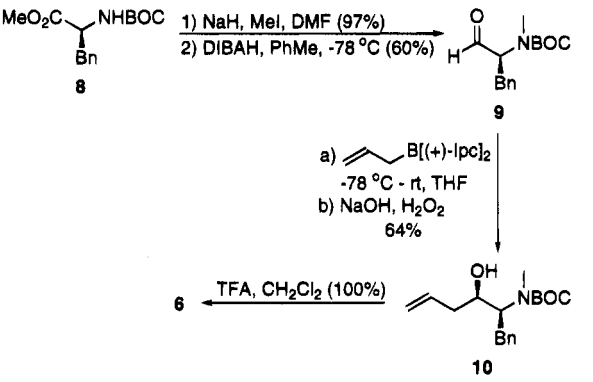
Scheme 1



Scheme 2



Scheme 3



(1) For reviews, see: (a) Simon, S. M.; Schindler, M. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3497. (b) Gottesman, M. M.; Pastan, I. *Annu. Rev. Biochem.* **1993**, *62*, 385.

(2) Stratmann, K.; Burgoyne, D. L.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1994**, *59*, 7219.

(3) For a review, see: Marquarding, D.; Gokel, G.; Hoffmann, P.; Ugi, I. In *Isonitrile Chemistry*; Ugi, I., Ed.; Academic Press: New York, 1971; pp 133–143.

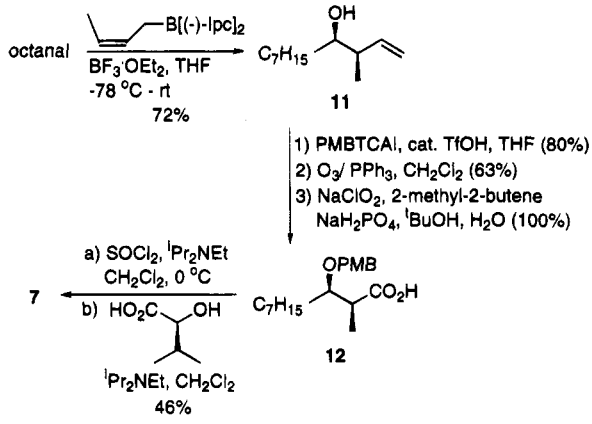
(4) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906.

(5) To minimize racemization of aldehyde **9**, solvents were removed from **9** at ≤30 °C and flash chromatography with silica gel was done in <30 min.

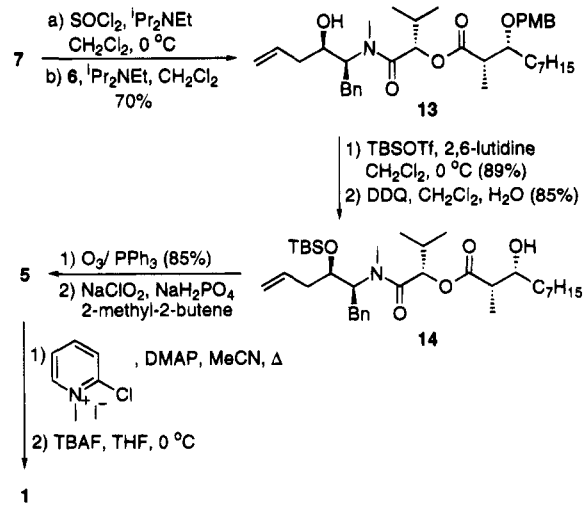
(6) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432.

0022-3263/95/1960-8118$09.00/0

Scheme 4



Scheme 5



illustrated in Scheme 4. Brown allylboration[7] of octanal furnished homoallylic alcohol **11** in 72% yield and 90% de.[8] The hydroxyl group was protected with *p*-methoxybenzyl 2,2,2-trichloroacetimidate (PMBTCAI)[9,10] in 80% yield, and the olefin was ozonized to the aldehyde (63% yield). Oxidation of the aldehyde with sodium chlorite[11] afforded acid **12** (100% yield). The acid was converted to the acid chloride which reacted with (*S*)-α-hydroxyisovaleric acid to produce ester acid **7** (46% yield).

Six steps after coupling of fragments **6** and **7** provided hapalosin (Scheme 5). Amide **13** was formed by reacting amino alcohol **6** with the acid chloride derivative of ester acid **7** (70% yield). The hydroxyl group was protected[12] with TBSOTf (89% yield), and the PMB ether was deprotected with DDQ (85% yield). Alkenol **14** was ozonized (85% yield), and the aldehyde was oxidized to the acid with sodium chlorite. Macrolactonization of crude hydroxy acid **5** under modified Mukaiyama conditions[13] and deprotection of the TBS ether of the resulting macrolide with TBAF produced hapalosin (**1**) in 13% yield for the final three steps.[14] Synthetic hapalosin was identical in all respects (^{1}HMR, ^{13}CMR, $[\alpha]_D$, IR, and HRMS) to the natural product.

Hapalosin was reported by Moore to exist as an approximately 3:1 mixture of conformers in $CDCl_3$ at room temperature. Two-dimensional NOESY analysis of synthetic hapalosin showed a strong correlation between the methine hydrogen α to nitrogen and the isobutyl hydrogen α to oxygen for the major conformer, indicative of an *s-cis* amide. No such correlation was found for the minor conformer. Analysis of the ground state conformations of hapalosin and its non-*N*-Me analog (which could potentially be synthesized via an intramolecular Passerini reaction) and their relationship to biological activity is currently underway.

Acknowledgment. Expanded ^{1}HMR spectra of the natural product from Prof. Moore and financial support from UCLA and NIH Grant GM51095 are gratefully acknowledged.

Supporting Information Available: Experimental procedures, ^{1}H NMR and ^{13}C NMR spectra, and $[\alpha]_D$, IR, and HRMS data for compounds **5**–**14** and synthetic hapalosin (7 pages).

JO951742R

(7) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919. (b) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535.

(8) Subsequent formation of a single diastereomer of esteracid **7** proved that the ee of alcohol **11** was >95%.

(9) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.

(10) TBS (see **4**) was not employed because side reactions competed with the deprotection of the TBS ether in the latter part of the synthesis.

(11) Hillis, L.; Ronald, R. *J. Org. Chem.* **1985**, *50*, 470.

(12) Preliminary attempts to macrolactonize the diolacid corresponding to **5** were unsuccessful.

(13) The original Mukaiyama conditions are in: Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, *49*. The modification of Mukaiyama conditions is based on Evans' modification of Keck conditions for macrolactonization with DCC: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(14) Investigatory trials with various other methods of macrolactonization did not appear to give better results. Amelioration in the macrolactonization is being sought.