ORGANIC LETTERS

2004
Vol. 6, No. 7
1103−1106

Efficient Solid-Phase Synthesis of Clavulones via Sequential Coupling of α- and ω-Chains

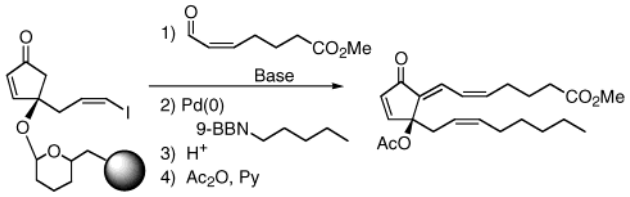
Hiroshi Tanaka,[†] Tsuyoshi Hasegawa,[†] Makoto Iwashima,[‡,§] Kazuo Iguchi,[‡] and Takashi Takahashi*[,†]

Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro, Tokyo 152-8552, Japan, and School of Life Science, Tokyo University of Pharmacy and Life Science, 1432-1, Horinouchi, Hachioji-Shi

ttak@apc.titech.ac.jp

Received December 4, 2003

ABSTRACT



We describe an efficient solid-phase synthesis of clavulones via the sequential coupling of the α- and ω-chains, involving two separate carbon–carbon bond-forming steps. The tetrahydropyranyl linker survived these reaction conditions and was cleaved without decomposing the unstable cross-conjugated dienones. Our methodology has allowed us to prepare six clavulone derivatives that are varied within the α-chain.

Chemical genetics is an effective methodology for the elucidation of gene and protein function, in which biologically active small molecules are used as biomolecular probes.[1] Biologically active natural products and their derivatives are often effective probes, as their structures have already been fine-tuned to bind to their target proteins in vivo during evolution.[2] Therefore, the high-speed synthesis of natural product-like libraries should lead to the rapid development of chemical probes that target proteins.[3,4]

Cross-conjugated dienone prostanoids such as Δ^7-prostaglandin A_1 methyl ether (**1**) display varied biological activities.[5] The mechanism of their action is considered to be based upon the reversible alkylation of certain proteins at the C11 position (Figure 1). 12-Acetoxyl cyclopentenone

[†] Tokyo Institute of Technology.
[‡] Tokyo University of Pharmacy and Life Science.
[§] Current address: Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, 2630, Sugitani, Toyama, Toyama 930-0194, Japan.

(1) (a) Schreiber, S. L. *Bioorg. Med. Chem.* **1988**, *6*, 1127−1152. (b) Stockwell, B. R.; Hardwick, J. S.; Tong, J. K.; Schreiber, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10662−10663.

(2) Tietze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996−4028.

(3) For a recent review of the synthesis of a natural product-like library, see: (a) Nielsen, J. *Curr. Opin. Chem. Biol.* **2002**, *6*, 297−305.

(4) For our reports of the combinatorial synthesis of small-molecule libraries based on the structure of biologically active natural products, see: (a) Doi, T.; Hijikuro, I.; Takahashi, T. *J. Am. Chem. Soc.* **1999**, *121*, 6749−6750. (b) Hijikuro, I.; Doi, T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716−3722. (c) Matsuda, A.; Doi, T.; Tanaka, H.; Takahashi, T. *Synlett* **2001**, 1101−1104. (d) Tanaka, H.; Zenkoh, T.; Setoi, H.; Takahashi, T. *Synlett* **2002**, 1427−1430. (e) Tanaka, H.; Ohno, H.; Kawamura, K.; Ohtake, A.; Nagase, H.; Takahashi, T. *Org. Lett.* **2003**, *5*, 1159−1162. (f) Tanaka, H.; Moriwaki, M.; Takahashi, M. *Org. Lett.* **2003**, *5*, 3807−3809. (g) Tanaka, H.; Amaya, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 3053−3057. (h) Takahashi, T.; Nagamiya, H.; Doi, T.; Peter, G.; Griffiths, P. G.; Bray, A. M. *J. Comb. Chem.* **2003**, *5*, 414−428. (i) Takahashi, T.; Kusaka, S.; Doi, T.; Sunazuka, T.; Omura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5230−5234.

(5) Suzuki, M.; Mori, M.; Niwa, T.; Hirata, R.; Furuta, K.; Ishikawa, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 2376−2385.

(6) (a) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171−5174. (b) Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Akutsu, H.; Kyogoku, Y.; Kitagawa, I. *Tetrahedron Lett.* **1982**, *23*, 5331−5334.

10.1021/ol036361b CCC: $27.50
Published on Web 03/09/2004

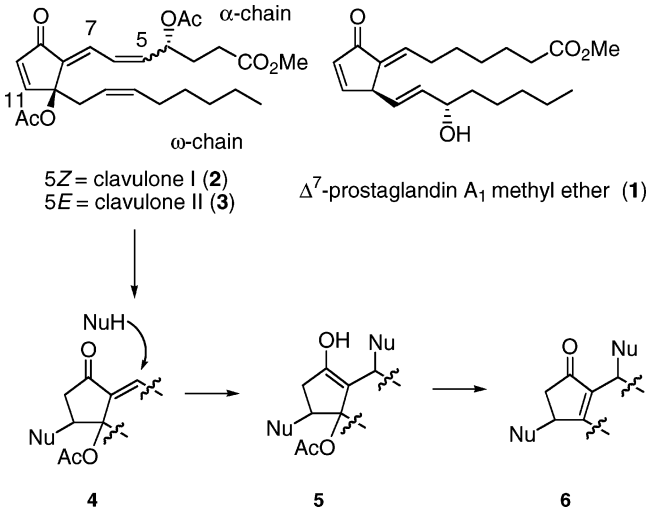
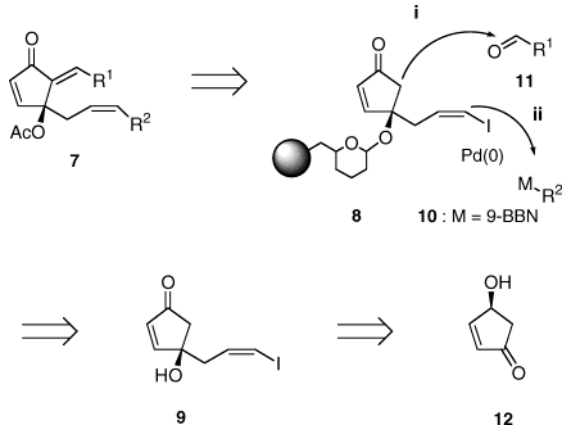


Figure 1. Structure of Cross-Conjugated Dienone Prostanoids **1**−**3**.

prostanoids such as clavulone I (**2**) and II (**3**)[6] are particularly interesting, as they show strong cytotoxicity. In clavulones, the sequential Michael addition at the C11 and C7 positions could potentially be irreversible, as the enol **5** generated by double Michael addition via **4** could undergo a subsequent β-elimination of the C12 acetoxyl group to provide enone **6**. The irreversible reaction would be much more effective at strongly inhibiting or modulating protein functioning compared to the reversible reaction. Therefore, clavulone derivatives bearing the appropriate side-chains could be interesting biochemical probes. Unfortunately, however, all syntheses of the 12-acetoxyl-cyclopentenone prostanoids are based upon traditional solution-phase methodology,[7] and none have been prepared by solid-phase technologies.

Solid-phase synthesis is an attractive method for the high-speed synthesis of small molecule libraries,[8] and recent developments in solid-phase synthesis are now permitting carbon−carbon bond formation on solid supports besides amide bond formation.[9] There have been several reports of polymer-supported or solid-phase synthesis of prostanoids.[10]

Scheme 1



However, these methodologies provide 2,3-substituted 4-hydroxyl cyclopentanone derivatives. Therefore, the solid-phase synthesis of clavulone derivatives with varying side-chains should be attractive and challenging. Herein, we describe an effective solid-phase synthesis of cross-conjugate prostanoids that is based upon incorporation of the α- and ω-chains via sequential carbon−carbon bond formation.

Our strategy for the solid-phase synthesis of clavulones **7** involves the (i) palladium-catalyzed coupling reaction of the solid-supported *cis*-vinyl iodide **8** with alkylborane **10** to afford stereoselectively the cis-configured ω-chain and (ii) aldol reaction of cyclic and acyclic aldehydes **11** with the cyclopentenone to form the cross-conjugated dienone system (Scheme 1). The unstable dienone core is elaborated at the final stages of the solid-phase synthesis. Significantly, the two carbon−carbon bond-forming steps can be realized without protecting group manipulations. The cyclopentenone core **8** is immobilized at the C12 *tert*-hydroxyl group via a tetrahydropyranyl linker, which is stable to the two sets of reaction conditions. Cleavage from the solid-support under mildly acidic conditions, followed by acetylation of the resultant *tert*-alcohol, provides the clavulone derivatives **7**. Optically active cyclopentenone **9** can additionally be prepared from (*S*)-4-hydroxycyclopentenone (**12**).

The preparation of cyclopentenone **9** bearing a *cis*-vinyl iodide is shown in Scheme 2. Treatment of cyclopentenone **12** with 3-trimethylsilyl-2-propynyllithium in THF at −78 °C gave stereoselectively diol **13** in 75% yield without racemization.[11] Protection of the two hydroxyl groups in **13** with triethysilyl chloride and triethylamine provided disilyl ether **14**; this was followed by iodination of the terminal acetylene with $AgNO_3$/NIS to afford iodoalkyne **15** in 90%

(7) (a) Corey, E. J.; Mehrotra, M. *J. Am. Chem. Soc*. **1984**, *106*, 3384. (b) Nagaoka, H.; Miyakoshi, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 3621−3624. (c) Hashimoto, S.; Arai, Y.; Hamanaka, N. *Tetrahedron Lett.* **1985**, *26*, 2679−2682. (d) Shibasaki, M.; Ogawa, Y. *Tetrahedron Lett.* **1985**, *26*, 3841−3844. (e) Ciufolini, M. A.; Zu, S. *J. Org. Chem.* **1998**, *63*, 1668−1675. (f) Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 3131−3132. (g) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1997**, 255−256. (h) Zhu, J.; Yang, J.-Y.; Klunder, A. J. H.; Liu, Z.-Y.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5847−5870. (i) Tius, M. A.; Hu, H.; Kawakami, J. K.; Busch-Petersen, J. *J. Org. Chem.* **1998**, *63*, 5971−5976. (j) Akhmetavaleev, R. R.; Baibulatov, G. M.; Nuriev, I. F.; Miftakhov, M. S. *Russ. J. Org. Chem.* **2001**, *37*, 1079−1082. (k) Akhmetavaleev, R. R.; Baibulatov, G. M.; Nuriev, I. F.; Shitikova, O. V.; Miftakhov, M. S. *Russ. J. Org. Chem.* **2001**, *37*, 1083−1087. (l) Roulland, E.; Monneret, C.; Florent, J.-C. *J. Org. Chem.* **2002**, *67*, 4399−4406. (m) Kuhn, C.; Skaltsuounis, L.; Monneret, C.; Florent, J.-C. *Eur. J. Org. Chem.* **2003**, 2585−2595 and references therein

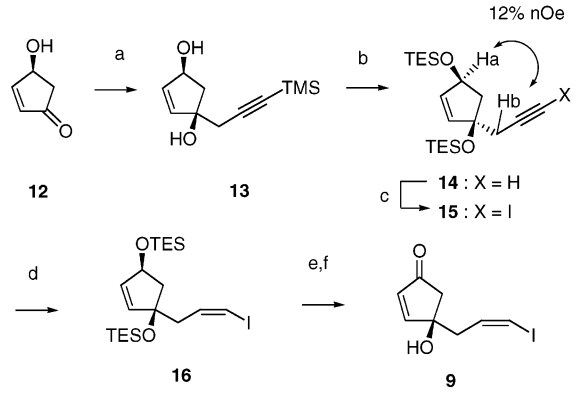
(8) (a) Sencei, P. *Solid-Phase Synthesis and Combinatorial Technology*; Wiley-Interscience: New York, 2000. (b) Dorwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH: New York; 2000. (c) Roland, E. D. *J. Comb. Chem*. **2002**, 369−418. (d) *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weinheim; 2002; Vols. 1 and 2.

(9) (a) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1582. (b) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202.

(10) (a) Chen, S.; Janda, K. D. *J. Am. Chem. Soc*. **1997**, *119*, 8724−8725. (b) Thompson, L. A.; Moore, F. L.; Moon, Y.-C.; Ellman, J. A. *J. Org. Chem*. **1998**, *63*, 2066−2067. (c) Lee, K. J.; Angulo, A.; Ghazal, P.; Janda, K. D. *Org. Lett.* **1999**, *1*, 1859−1862. (d) Manzotti, R.; Thag, S.-Y.; Janda, K. D. *Tetrahedron* **2000**, *56*, 7885−7892. (e) Dragoli, D. R.; Thompson, L. A.; O'Brien, J.; Ellman, J. A. *J. Comb. Chem*. **1999**, *1*, 534−539.

(11) Optical purity of **13** was estimated by ^{1}H NMR analysis of the corresponding MTPA ester of the secondary alcohol to be >98%ee.

Scheme 2[a]

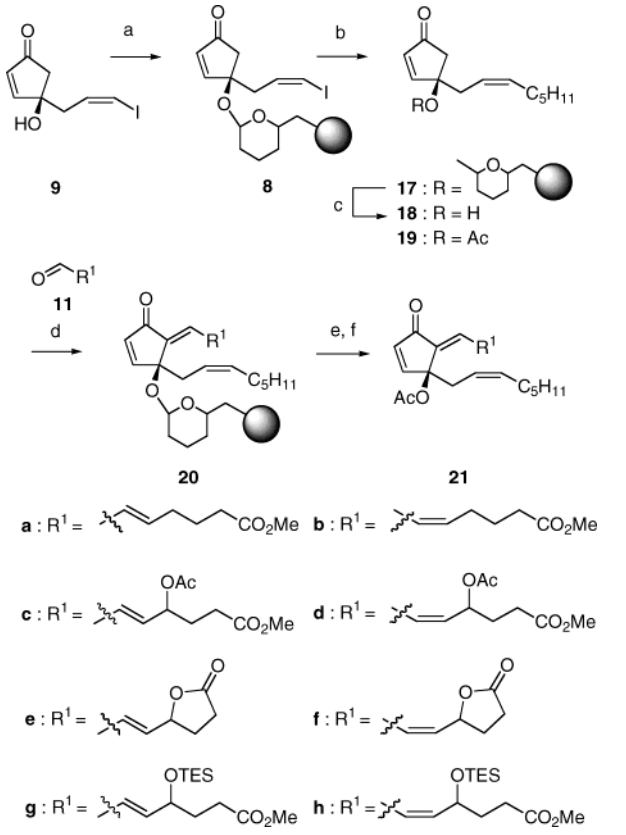


[a] Reagents and conditions: (a) 1-trimethylsilyl-1-propyne, lithium diisopropyl amide, THF, −78 °C, 85%; (b) triethylsilyl chloride, imidazole, CH_2Cl_2, rt; (c) $AgNO_3$, *N*-iodosuccinimide, rt, 83% for two steps; (d) Cy_2BH, Et_2O, rt, then AcOH, 82%; (e) CSA, MeOH, 0 °C; (f) MnO_2, CH_2Cl_2/benzene (1/2), rt, 75% for two steps.

yield (two steps). Structure determination of **15** was achieved by analysis of ^{1}H NOE spectra. Stereoselective reduction of the iodoalkyne was accomplished by hydroboration followed by acid hydrolysis of the vinyl borane to yield the *cis*-vinyl iodide **16** in 73% yield.[12] Removal of the two triethysilyl ethers was achieved under mildly acidic conditions and followed by a selective oxidation of the resultant secondary hydroxyl with manganese dioxide to provide ketone **9** in 93% yield (two steps).

Immobilization of ketone **9** on solid-support (Scheme 3) was achieved by exposing a 0.5 M CH_2Cl_2 solution of alcohol **9** to 3,4-dihydro-2*H*-pyran (DHP) polystyrene (0.72 mmol/g)[13] with pyridinium *p*-toluenesulfonate (PPTS) at 40 °C; the product of the reaction was the solid-supported ketone **8**. Treatment of **8** under mild aqueous acidic conditions resulted in the recovery of **9** in 75% yield based upon the resin loading. With **8** in hand, and its structural integrity confirmed, the two side-chains were sequentially introduced. Treatment of the solid-supported vinyl iodide **8** with Pd(PPh$_3$)$_4$, 2 M aq Na_2CO_3, and pentyl 9-9-borabicyclo[3.3.1]-nonane (9-BBN), prepared by in situ hydroboration of 1-pentene, provided solid-supported 4-substituted cyclopentenone **17** in 78% yield;[14] its structure was confirmed by purification of the released ketone **18**. Aldol condensation of the solid-supported ketone **17** to couple the α-chain was examined using aldehydes **11a** and **11b**. Exposure of the solid-supported ketone **17** to a THF solution of potassium hexamethyldisilazide (KHMDS) at −78 °C for 40 min, followed by addition of aldehyde **11a**, provided the solid-supported trienones **20a**. Cleavage from the resin under mildly acidic conditions, followed by acetylation, provided

Scheme 3[a]



[a] Reagents and conditions: (a) 3,4-dihydro-2*H*-pyran-2-yl-methoxymethyl polystyrene, PPTS, CH_2Cl_2, 40 °C, 20 h; (b) pentanyl 9-BBN, Pd(PPh$_3$)$_4$, 2 M Na_2CO_3 (aq), THF, 45 °C, 12 h; (c) TFA/CH_2Cl_2, rt, 30 min; (d) KHMDS, THF, −78 °C, then **8a**−**h,** −78 °C, 2 h; (e) TFA/CH_2Cl_2, rt, 30 min; (f) Ac_2O, Py., DMAP, rt, 2 h.

the corresponding cross-conjugate dienone **21a** in 52% yield along with ketone **19** in 15% yield. Lithium diisopropylamide (LDA), which has been used in the reported solution-phase syntheses of clavulones, did not work well for the solid-phase synthesis. Subjection of the (*Z*)-aldehyde **11b** to these reaction conditions resulted in partial isomerization of the double bond to provide **21b** in 45% yield along with the (*E*)-isomer **21a** in 7% yield. Further examination using the isolated (*Z*)-isomer **21b** revealed that isomerization of the double bond occurred under the mildly acidic cleavage conditions.

To demonstrate the applicability of this solid-phase synthesis, we conducted the solid-phase synthesis of clavulone and clavulolactone-related compounds (Scheme 3 and Table 1). Aldol reaction using aldehydes **11c** and **11d** provided the corresponding coupled products **21c** and **21d** in moderate yield. However, coupling with the two cyclic aldehydes **11e** and **11f** did not provide the corresponding clavulolactones **21e** and **21f** under the same reaction conditions due to the instability of the cyclic aldehydes **11e** and **11f** under the basic conditions. To overcome this problem, we designed the acyclic silyoxy aldehydes **11g** and **11h**. Deprotection of the silyl ether followed by cyclization under

(12) Corey, E. J.; Cashman, J. R.; Eckrich, T. M.; Corey, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 713−715.
(13) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333−9336.
(14) (a) Suzuki, A.; Miyaura, N.; Ishikawa, T.; Sasaki, H.; Ishikawa, M.; Satoh, M. *J. Am. Chem. Soc.* **1989**, *111*, 314−321. (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.

Table 1. Solid-Phase Synthesis of Clavulone Derivatives **21**

entry	aldehyde	product	*E*/*Z* ratio	yield[a] (%)
1	**11c**	**21c**	*E* only	52%
2	**11d**	**21d**	1:11[b]	55%
3	**11e**	**21e**		0%
4	**11f**	**21f**		0%
5	**11g**	**21e**	*E* only	44%
6	**11h**	**21f**	1:10[b]	49%

[a] Isolated yield is based on the solid-support ketone **17**. [b] Ratio was calculated on the basis of the isolated yields.

the acidic release conditions provided the γ-butanolide derivatives. The aldol condensation of each of the aldehydes **11g** and **11h** with ketone **17**, followed by acetylation after cleavage under acidic conditions, provided the lactones **21e** and **21f** in 44 and 49% yields, respectively. A small amount of (*E*)-olefin **21e** was observed when (*Z*)-olefin **11h** was used. Further purification of diastereomer **21c** was performed by HPLC to give clavulone II (**3**). The analytical data (^{1}H NMR, ^{13}C NMR, HR-MS) of the synthetic clavulone II were identical to those of the isolated material.[6a]

In summary, we have demonstrated an efficient solid-phase synthesis of clavulone derivatives by a reaction sequence involving palladium-catalyzed coupling and aldol condensation. Using this flexible methodology, the synthesis of six clavulones was accomplished. The biological activity of the clavulone derivatives is currently being explored. The synthesis of a combinatorial library of clavulones is in progress.

Acknowledgment. This work was supported by a Grand-in-Aid for Scientific Research on a Priority Area (S) from the Ministry of Education, Culture, Sports, Science, and Technology. (Grant-in-Aid No. 14103013).

Supporting Information Available: Experimental procedures for synthesis and full characterization for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036361B