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A Cobalt-Complexed Propynal in Organic Synthesis: A Highly Stereoselective Total Synthesis of Bengamide E†

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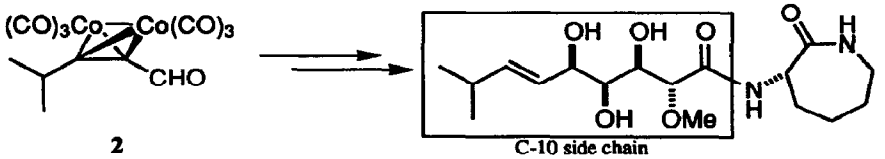
Abstract: A highly stereoselective aldol reaction of the cobalt-complexed 4-methylpent-2-ynal **2** with *O*-silyl ketene *O,S*-acetal **3** provided the *syn*-aldol product, which was subsequently converted to (+)-bengamide E through optical resolution and the second diastereoselective aldol reaction as crucial steps.

Several bengamides, novel amino acid derivatives, have recently been isolated from a Choristid sponge collected in Fiji Islands.[1] Bengamides thus obtained have been shown to possess significant antihelminthic activity as well as cytotoxicity. (2*R*,3*R*,4*S*,5*R*,6*E*)-3,4,5-Trihydroxy-2-methoxy-8-methylnon-6-enoyl side chain (C-10 side chain) was elucidated as a common structural feature of bengamide family. Therefore, stereoselective construction of the C-10 side chain involving four contiguous stereogenic centers would be the most crucial point to develop a general procedure for the total synthesis of bengamide family. Several groups have already accomplished total syntheses of bengamide E,[2] B,[2b] and A[3], and the C-10 side chain,[4] starting from natural resources like cyclitol,[2a,3] glucose,[2b,c,4] tartaric acid[2d] and glyceraldehyde.[2e] We describe in this letter a highly stereoselective construction of the C-10 side chain as well as a total synthesis of bengamide E (**1**), a representative of bengamide family having the simplest cyclic lysine component, from the cobalt-complexed propynal **2** *via* dual highly selective aldol reactions.[5]

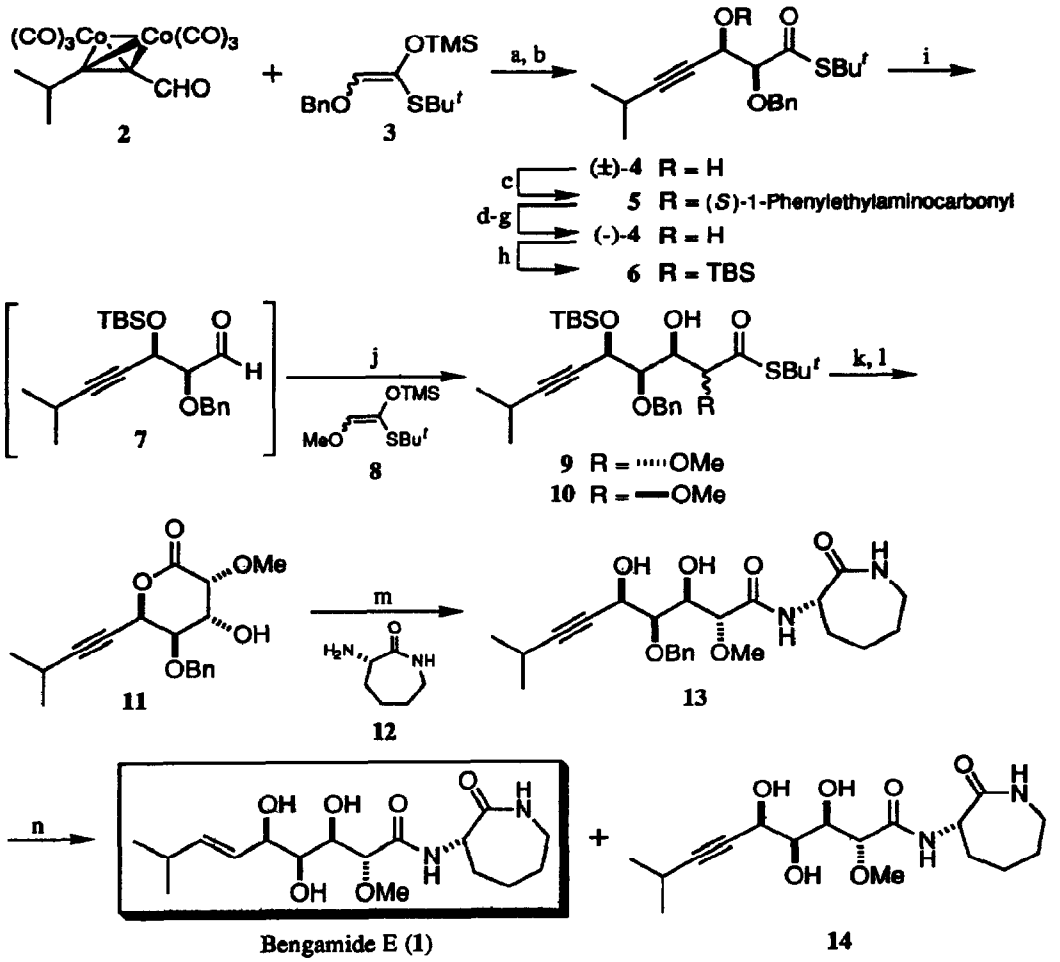


2 C-10 side chain

Bengamide E (**1**)

As our point of departure, we took the cobalt-complexed 4-methylpent-2-ynal **2** as a starting material since the cobalt-complexed propynals have recently been shown to be excellent substrates for highly *syn*-

† This paper is dedicated to Professor Yasumitsu Tamura on the occasion of his 70th birthday.



(a) $BF_3 \cdot OEt_2$, CH_2Cl_2, -78°C; (b) CAN, MeOH, 0°C, 83 % from 2 (*syn* : *anti* = 95 : 5); (c) (*S*)-1-phenylethyl isocyanate, *N*,*N*-dimethylethanolamine, benzene, reflux; (d) $Co_2(CO)_8$, Et_2O; (e) separation by column chromatography; (f) CAN, MeOH, 0°C; (g) $HSiCl_3$, benzene, r.t., 30 % from (±)-4; (h) TBSCl, imidazole, DMF, r.t., 89 %; (i) DIBAL, CH_2Cl_2, -78°C; (j) $SnCl_4$, CH_2Cl_2, -78°C then 7, 68 % from 6 (9 : 10 = 92 : 8); (k) HCl, THF, H_2O, r.t.; (l) $AgOCOCF_3$, THF, 50°C, 74 % from 9; (m) Et_3N, dioxane, r.t., 91 %; (n) Na, NH_3, THF, -78°C, 62 %.

selective aldol reaction with *O*-silyl ketene *O,S*-acetals.[5] Thus the cobalt complex **2**, easily prepared from 4-methylpent-2-yn-1-ol[6] by two steps [(i) PCC oxidation, (ii) cobalt complexation with $Co_2(CO)_8$], was allowed to react with *O*-silyl ketene *O,S*-acetal **3** (*E* : *Z* = 27 : 73), derived from *S-tert*-butyl benzyloxyethanethioate in the presence of boron trifluoride etherate (BF_3•OEt_2) in dry methylene chloride at -78°C. The resulting aldol condensation products with cobalt moiety were subsequently decomplexed with cerium(IV) ammonium nitrate (CAN) in methanol at 0°C to afford *syn*-isomer (±)-**4** in a highly diastereoselective fashion (83 %, *syn* : *anti* = 95 : 5). Optical resolution of (±)-**4** was easily achieved as follows. *S*-(-)-1-Phenylethylaminocarbonyl group was introduced on the β-hydroxy group of (±)-**4** to give an inseparable diastereomixture, which was converted into a mixture of the corresponding cobalt-complexed compounds by $Co_2(CO)_8$ treatment. Chromatographic separation, consecutive demetalation and removal of carbamate moiety[7] provided (-)-**4** {$[\alpha]_D^{24}$ -87.1° (*c* 1.0, $CHCl_3$)} and (+)-**4** {$[\alpha]_D^{18}$ +85.6° (*c* 1.0, $CHCl_3$)} in 60 % overall yield [(-)-**4** : (+)-**4** = 50 : 50] from (±)-**4**.[8] It should be mentioned that cobalt complexation of the carbamates **5** enabled us to isolate each enantiomer by chromatography without any trouble.

With chiral *syn*-aldol product (-)-**4** with two requisite stereogenic centers in hand, we turned our effort to elaboration of (-)-**4** to the C-10 side chain. β-Hydroxy group of (-)-**4** was protected with *tert*-butyldimethylsilyl chloride to furnish **6** (89 %). Reduction of **6** with diisobutylaluminum hydride afforded the aldehyde **7**, which was immediately exposed to the aldol reaction under the chelation-controlled condition with stannyl enolate,[9] prepared *in situ* from *O*-silyl ketene *O,S*-acetal **8** (*E* : *Z* = 25 : 75) and stannyl(IV) chloride, to yield the aldol product **9** along with its 2-epimer **10** (**9** : **10** = 92 : 8)[10] in 68 % overall yield from **6**. This stereoselective aldol reaction furnished all carbon framework required for the synthesis of the C-10 side chain of bengamides with correct stereochemistry.

The next phase of our synthesis of bengamide E faced some modifications of **9** and a coupling with the cyclic lysine derivative. Prior to a coupling with cyclic lysine derivative **12**, the aldol product **9** was transformed into the corresponding δ-lactone **11** in 74 % yield by hydrolysis with hydrochloric acid and lactone formation with silver(I) trifluoroacetate.[11] The coupling reaction of **11** with (*S*)-α-amino-ε-caprolactam **12**[12] easily proceeded in the presence of triethylamine in dioxane without protection of the C-3 hydroxy group to give the condensation product **13** in 91 % yield. The Birch reduction (Na / NH_3) of **13** effected simultaneous removal of benzyl group on the C-4 hydroxy group of the side chain and reduction of the triple bond to *trans*-double bond to provide bengamide E (**1**) {$[\alpha]_D^{22}$ +24° (*c* 0.1, MeOH), lit.[2a] $[\alpha]_D^{29}$ +25° (*c* 0.29, MeOH)}. The alkyne derivative **14**, a presumable intermediate in a conversion of **13** to **1**, could also be isolated as a by-product. After transformation of the minor product **14** into the desired **1** under the same Birch condition, (+)-bengamide E was finally obtained in a 62 % combined yield from **13**. Synthetic (+)-bengamide E was unambiguously proved to be identical with authentic specimen by comparison with ^1H and ^{13}C NMR spectra.

Thus, we have completed a highly stereocontrolled synthesis of bengamide E (**1**), starting from the cobalt-complexed 4-methylpent-2-ynal derivative **2**. The newly developed procedure described here would open up an alternative way for the preparation of bengamide family.

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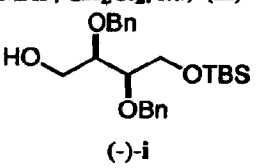
REFERENCES AND NOTES

1. (a) Quiñoà, E.; Adamczeski, M.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4494. (b) Adamczeski, M.; Quiñoà, E.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 647. (c) Adamczeski, M.; Quiñoà, E.; Crews, P. *J. Org. Chem.* **1990**, *55*, 240.
2. (a) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 1063. (b) Broka, C. A.; Ehrler, J. *Tetrahedron Lett.* **1991**, *32*, 5907. (c) Kishimoto, H.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1992**, *57*, 5042. (d) Marshall, J. A.; Luke, G. P. *Synlett* **1992**, 1007. (e) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1993**, *58*, 6229.
3. Chida, N.; Tobe, T.; Okada, S.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1064.
4. Gurjar, M. K.; Srinivas, N. R. *Tetrahedron Lett.* **1991**, *32*, 3409.
5. Mukai, C.; Kataoka, O.; Hanaoka, M. *Tetrahedron Lett.* **1991**, *32*, 7553.
6. (a) Hoffmann, R. W.; Julius, M. *Liebigs Ann. Chem.* **1991**, 811. (b) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 2747.
7. Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2781.
8. ^{1}H NMR analysis of (-)- and (+)-**4** in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III) indicated that each isomer is free from contamination with its enantiomeric isomer. The absolute configuration of *syn*-aldol products were determined as designated by independent chemical transformation to 2,3-bis(benzyloxy)-4-*tert*-butyldimethylsilyloxybutan-1-ol (-)-**i** {$[\alpha]_D^{22}$ -14.4° (*c* 0.5, $CHCl_3$)} and (+)-**i** {$[\alpha]_D^{20}$ +13.9° (*c* 0.5, $CHCl_3$)} from (-)-**4** and (+)-**4**, respectively, by four steps [(i) $LiAlH_4$, THF, reflux; (ii) TBSCl, Et_3N, DMAP, CH_2Cl_2, r.t.; (iii) NaH, THF, 0°C then BnBr, $^nBu_4NI$, 0°C → r.t.; (iv) O_3, MeOH, -78°C then $NaBH_4$, 0°C]. The authentic sample of (+)-**i** {$[\alpha]_D^{17}$ +13.3° (*c* 0.5, $CHCl_3$)} was derived from dimethyl L-tartrate by three steps [(i) NaH, THF, 0°C then BnBr, $^nBu_4NI$, 18-crown-6, 0°C → r.t.; (ii) $LiAlH_4$, THF, reflux; (iii) NaH, THF, r.t. then TBSCl].



(-)-**i**

9. Gennari, C.; Beretta, M. G.; Bernardi, A. Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893.
10. The stereochemistry of four contiguous chiral centers of **9** was tentatively assigned on the basis of ^{1}H NMR spectral consideration of the lactone **11**. Furthermore, conversion of **11** to (+)-bengamide E unambiguously confirmed the assignment of stereochemistry.
11. Masamune, S.; Hayase, Y.; Schiling, W.; Chan, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756.
12. Pellegata, R.; Pinza, M.; Pifferi, G. *Synthesis* **1978**, 614.

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