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A Practical Enantioselective Total Synthesis of the Bengamides B, E, and Z

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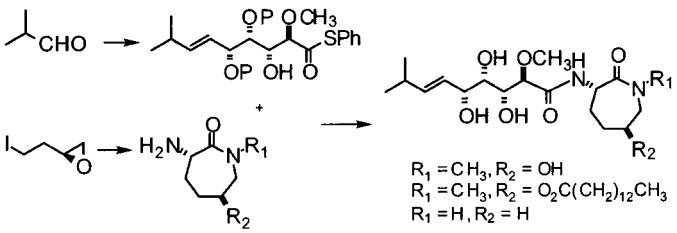
ABSTRACT



A practical total synthesis of Bengamides B, E, and Z from a common polyol intermediate is described. Consecutive aldol condensations afford a protected polyol thioester side chain suitable for coupling to the Bengamides. A novel chiral phase transfer catalyzed enantioselective alkylation affords the more highly functionalized amino caprolactams required for Bengamides B and Z. Use of the 2-naphthylmethyl ether protecting group, compatible with the boron Lewis acids required for enantioselective aldol condensation, allows direct access to Bengamide B.

Twenty-four natural bengamides have been isolated, principally from *Jaspis* sponges found in coral reefs near the Fiji Islands and Australia.[1] Some natural bengamides show potentially useful antiproliferative activity, having IC_{50} values for in vitro growth inhibition from 10 to 100 nM.[2] Notably, bengamides bearing myristate esters on the caprolactam are >100 times more potent in vitro than bengamide Z (**1**), a difference that may arise from poor cellular uptake of **1**.[2] Bengamide B (**2**) showed a unique profile in the NCI 60 cell line panel compared to standard antitumor agents, arresting growth at both G1/S and G2/M restriction points.[2c]

Recent work has been reported toward identification of the biological target(s) of the bengamides.[3] An analogue of bengamide B (**2**) is undergoing clinical trial as a therapeutic indicated for drug resistant solid tumors.[4]

The ongoing interest in bengamide analogues as clinical candidates for cancer chemotherapy has led to a number of total syntheses of the bengamides, principally bengamide E (**3**).[2a,5] Existing syntheses of bengamide B (**2**) are lengthy,

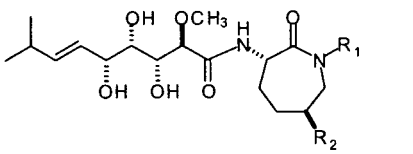


Figure 1.

(1) (a) Valadao, R. M.; Crews, P.; Thale, Z. *Abstracts of Papers*, 221st National Meeting of the American Chemical Society; American Chemical Society: Washington, DC, 2001; CHED-742. (b) Thale, Z.; Kinder, F. R.; Bair, K. W.; Bontempo, J.; Czuchta, A. M.; Versace, R. W.; Phillips, P. E.; Sanders, M. L.; Wattanasin, S.; Crews, P. *J. Org. Chem.* **2001**, *66*, 1733−1741. (c) Groweiss, A.; Newcomer, J. J.; O'Keefe, B. R.; Blackman, A.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 1691−1693. (d) Fernandez, R.; Dherbomez, M.; Letourneux, Y.; Nabil, M.; Verbist, J. F.; Biard, J. F. *J. Nat. Prod.* **1999**, *62*, 678−680. (e) D'Auria, M. V.; Giannini, C.; Minale, L.; Zampella, A.; Debitus, C.; Frostin, M. *J. Nat. Prod.* **1997**, *60*, 814−816. (f) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Org. Chem.* **1990**, *55*, 240−242. (g) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 647−654. (h) Quinoa, E.; Adamczeski, M.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4494−4497.

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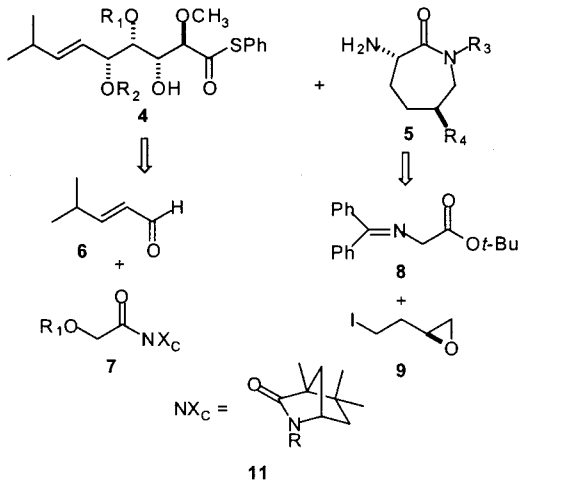
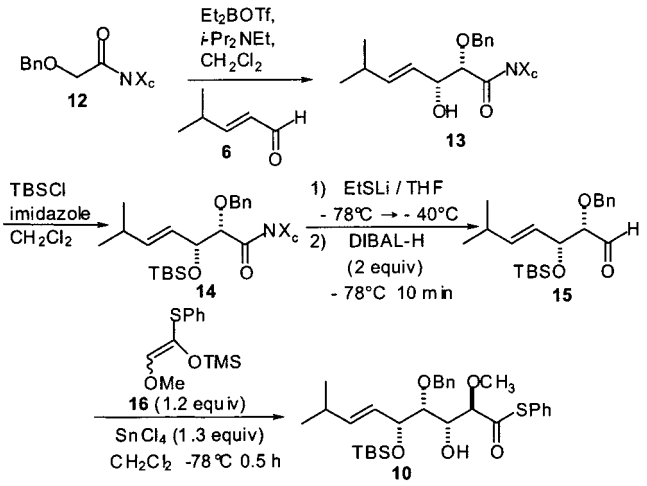
employ reagents impractical for use on larger scale, or suffer one or more low yielding steps that significantly reduce the overall yield, limiting throughput and increasing cost.[2a,5] Since all of the bengamides share a common polyol acid, we sought to develop a single short sequence to access the major structural subtypes of the bengamides differing only in the nature of the lactam coupling partner.

Scheme 1



As have all previous efforts, our construction of the bengamide skeleton relies on the coupling of two general subunits **4** and **5**. Remarkably, what we perceived as the most direct route to the polyol side chain **4**, via sequential *syn* and *anti* asymmetric aldol reactions beginning with the commercially available *E* enal **6**, had not been described,[2b,5] although an *anti* aldol construction had been utilized by Mukai on related protected alkyne analogues.[5c,d] An efficient sequence to amino caprolactam **5** was envisioned via enantioselective alkylation of the known imine **8** with iodoepoxide **9** and subsequent ring closure. An alternative, efficient sequence to the required caprolactams beginning with hydroxylysine was recently disclosed.[2a]

Scheme 2



Our route to benzyl-protected thioester **10** was initiated by acylation of the lithium salt of lactam **11** (R = Li) with benzyloxyacetyl chloride, affording the chiral imide **12**.[6] Generation of the *Z* boron enolate by treatment of **12** with Et_2BOTf[6,7] and condensation with commercial *E* enal **6**[8] at −50 °C afforded the expected *syn* aldol adduct **13** in >24:1 dr, which was immediately protected as TBS ether **14** in 80% overall yield from **12** (Scheme 2). The auxiliary was removed with EtSLi to give an intermediate ethyl thioester (95%) and **11** (R = H) (93%). The resulting thioester was reduced at −78 °C with DIBAL-H to give the sensitive aldehyde **15** in 91% yield. A variant of the chelation-controlled Gennari−Mukaiyama aldol reaction of **15** with phenylthioketene acetal **16** in the presence of $SnCl_4$ then afforded the required 2,3-*anti*, 3,4-*syn* aldol adduct **10** (73% of **10**) with 11.5:1 dr.[9,10] The diastereoselectivity obtained with **16** was superior to that of the related *tert*-butylthioketene acetal.[9]

The relative and absolute stereochemistry of **10** was readily confirmed by conversion to (+)-bengamide E (**3**) (Scheme 3). Heating a mixture of commercial (−)-α-amino-ϵ-caprolactam **17** and thioester **10** at reflux in dioxane effected coupling affording amide **18** (98%). Deblocking of protected bengamide E derivative **18** was effected by sequential Na/

(2) (a) Kinder, F. R.; Wattanasin, S.; Versace, R. W.; Bair, K. W.; Bontempo, J.; Green, M. A.; Lu, Y. J.; Marepalli, H. R.; Philips, P. E.; Roche, D.; Tran, L. D.; Wang, R.; Waykole, L.; Xu, D. D.; Zabludoff, S. *J. Org. Chem.* **2001**, *66*, 2118. (b) Kinder, F. R., Jr.; Versace, R. W.; Bair, K. W.; Bontempo, J. M.; Cesarz, D.; Chen, S.; Crews, P.; Czuchta, A. M.; Jagoe, C. T.; Mou, Y.; Nemzek, R.; Phillips, P. E.; Tran, L. D.; Wang, R.; Weltchek, S.; Zabludoff, S. *J. Med. Chem.* **2001**, *44*, 3692−3699. (c) Phillips, P. E.; Bair, K. W.; Bontempo, J.; Crews, P.; Czuchta, A. M.; Kinder, F. R.; Vattay, A.; Versace, R. W.; Wang, B.; Wang, J.; Wood, A.; Zabludoff, S. *Proc. Am. Assoc. Cancer Res.* **2000**, *41*, 59.

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(5) (a) Liu, W.; Szewczyk, J. M.; Waykole, L.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2002**, *43*, 1373−1375. (b) Banwell, M. G.; McRae, K. J. *J. Org. Chem.* **2001**, *66*, 6768−6774. (c) Mukai, C.; Moharram, S. M.; Kataoka, O.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2849−2854. (d) Mukai, C.; Kataoka, O.; Hanaoka, M. *J. Org. Chem.* **1995**, *60*, 5910−5918. (e) Chida, N.; Tobe, T.; Murai, K.; Yamazaki, K.; Ogawa, S. *Heterocycles* **1994**, *38*, 2383−2388. (f) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1993**, *58*, 6229−6234. (g) Chida, N.; Tobe, T.; Okada, S.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1992**, 1064−1066. (h) Kishimoto, H.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1992**, *57*, 5042−5044. (i) Broka, C. A.; Ehrler, J. *Tetrahedron Lett.* **1991**, *32*, 5907−5910. (j) Chida, N.; Tobe, T.; Ogawa, S. *Tetrahedron Lett.* **1991**, *32*, 1063−1066.

(6) Boeckman, R. K., Jr.; Connell, B. T. *J. Am. Chem. Soc.* **1995**, *117*, 12368−12369.

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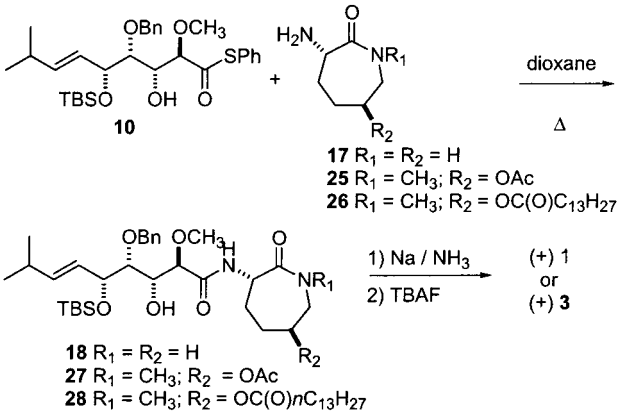
(8) Larger quantities of **6** were prepared by isomerization of the adduct of isobutyraldehyde and acetylene to **6** (81%): (a) Chodkiewicz, W. *Ann. Chim. (Paris) [13]* **1957**, *2*, 819−69. (b) Chabardes, P. *Tetrahedron Lett.* **1988**, *29*, 6253−6256.

(9) Gennari, C.; Grazia Beretta, M.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R. *Tetrahedron* **1986**, *42*, 893−909.

(10) Phenylthioketene acetal **16** was prepared as a variable but highly *E*-enriched *E*/*Z* mixture by treatment of the phenyl thioester of methoxyacetic acid with TMSOTf.[9] The diastereoselectivity of the subsequent aldol condensation did not depend on the *E*/*Z* ratio of **16**.

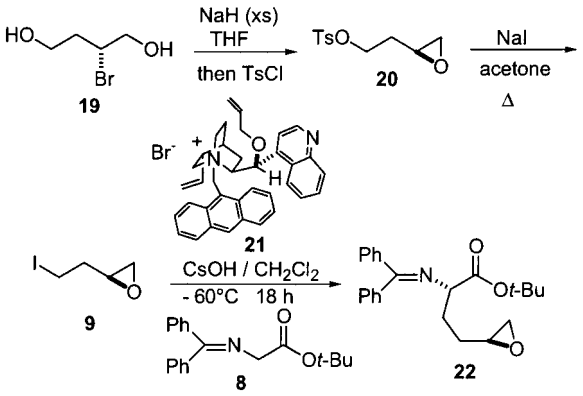
Scheme 3



NH_3 reduction and TBAF-mediated desilylation affording (+)-bengamide E (**3**) in 67% overall yield. Synthetic (+)-**3** was identical in all respects to an authentic sample of natural (+)-**3**.[2b]

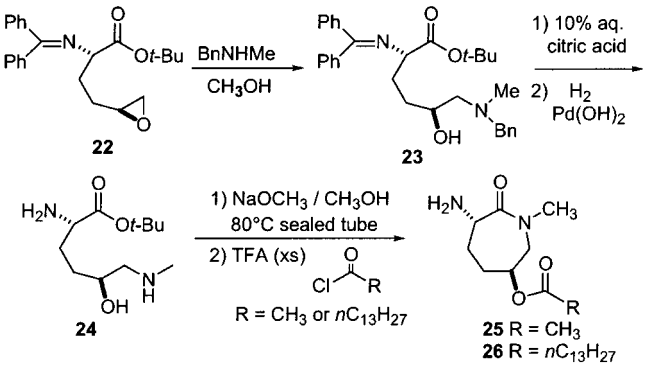
Our route to the more highly functionalized caprolactams present in bengamides B and Z employed the disconnections outlined in Scheme 1. Iodoepoxide **9** was derived from the diol **19**, which is available in two steps (70% overall) from D-aspartic acid.[11] Complete deprotonation of the diol **19** results in cyclization to the oxirane followed by trapping of the residual alkoxide with TsCl, affording epoxide **20** in 89% yield (Scheme 4). Tosylate **20** was transformed to iodoep-

Scheme 4



oxide **9** upon exposure to NaI in acetone (93%). Treatment of the commercial imine **8** and the iodoepoxide **9** with CsOH and 10 mol % of chiral phase transfer catalyst **21** at − 60 °C for 18 h afforded epoxy glycinate **22** in 83% yield as a single detectable diastereomer based upon 400 MHz NMR analysis.[12,13] Direct use of the tosylate proved to be unsatisfactory, as did use of the related known chiral iodoethyl acetonide.

Scheme 5



Acidic or Lewis acidic aminolysis conditions were unsatisfactory owing to competitive intramolecular epoxide opening by the imine nitrogen. Methanolic methylamine proved insufficiently nucleophilic to open the epoxy glycinate **22**; however, use of an excess of the more nucleophilic benzylmethylamine provided the required amino alcohol **23** in 98% yield (Scheme 5). Imine hydrolysis with 10% aqueous citric acid followed by debenzylation in the presence of Pearlman's catalyst afforded amino alcohol **24** (86% overall from **22**).[14] Heating **24** in a sealed tube with NaOMe in MeOH at 80 °C cleanly effected ring closure,[15] and the resulting hydroxy lactam was directly esterified with either acetyl chloride or myristryl chloride in the presence of excess TFA to give the key lactam subunits **25** (72%) and **26** (79%), respectively, (overall from **24**).[16]

Coupling of the polyol side chain **10** with the caprolactam **25** was carried out in the same manner as for bengamide E, affording amide **27** in 94% yield (Scheme 3). Reduction of **27** with Na/NH_3 not only removed the benzyl group but also cleaved the acetyl group, presumably by aminolysis, affording the pentaol silyl ether (74%). Direct treatment with TBAF then led to (+)-bengamide Z (**1**) (73%), after purification by reverse phase chromatography, which was identical in all respects to an authentic sample of natural (+)-bengamide Z (**1**).[2b]

Although coupling of **10** and **26** to afford amide **28** proceeded smoothly (Scheme 3), regrettably selective removal of the benzyl group in the presence of the myristyl ester could not be realized under a variety of reaction conditions using either reductive or oxidative methods.

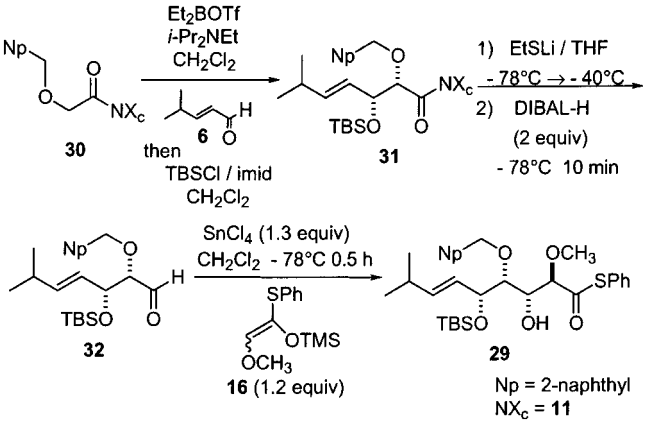
For example, oxidation of amide **28**, with DDQ resulted in poor conversion to the related benzoate, implying that oxidation of the intermediate hemiketal (or mixed ketal via proximal hydroxyl participation) was more rapid than the initial oxidation of the benzyl ether moiety.

Thus, a protecting group modification was required in order to access bengamide B (**2**). A *p*-methoxybenzyl (PMB) ether, an obvious choice, proved unsuitable owing to

(11) Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. M.; Rapoport, H. *Synthesis* **1992**, 621−623.
(12) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (b) Corey, E. J.; Noe, M. C. *Org. Synth.* S-982.
(13) Salt **21** (chloride) was recovered (85%) and reused as obtained.
(14) (a) Pearlman, W. M. *Tetrahedron Lett.* **1967**, 1663−1664. (b) Bernotas, R. C.; Cube, R. V. *Synth. Commun.* **1990**, *20*, 1209−1212.
(15) Ducrot, P.; Rabhi, C.; Thal, C. *Tetrahedron* **2000**, *56*, 2683−2692.
(16) Borgman, R. J.; McPhillips, J. J.; Stitzel, R. E.; Goodman, I. J. *J. Med. Chem.* **1973**, *16*, 630−633.

incompatibility with the Lewis acidic conditions of the boron enolate aldol reaction employed for polyol side-chain construction. After some consideration, we selected the recently described 2-naphthylmethyl group,[17] which appeared to represent a compromise between stability to Lewis acids and ease of removal under oxidative conditions.

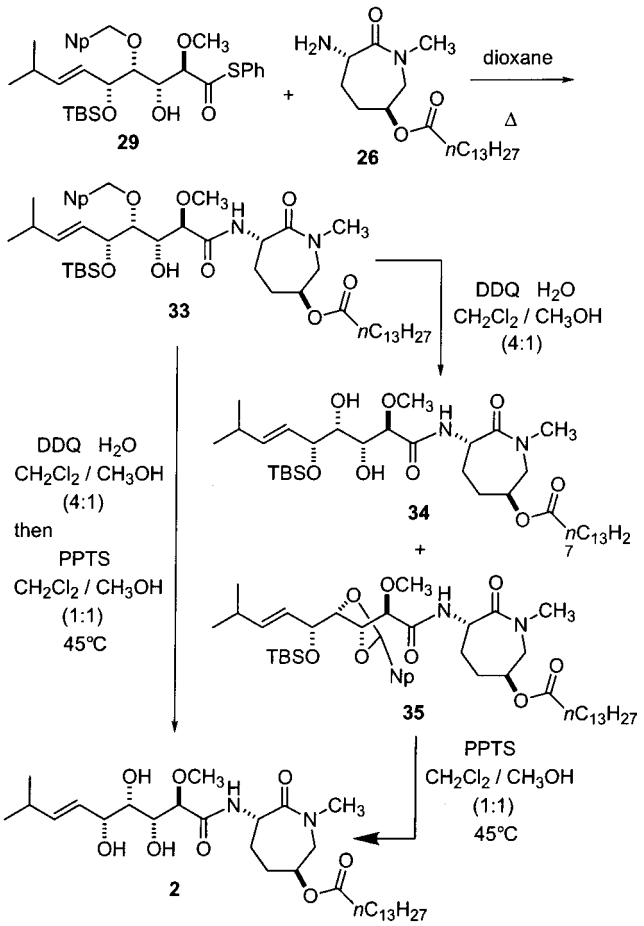
Scheme 6



2-Naphthylmethyl-protected thioester **29** was prepared in an analogous fashion to **10** (Scheme 6). Chiral imide **30**, available in two standard steps from ethyl glycolate (70% overall yield),[18] was converted to the diethylboron enolate and condensed with aldehyde **6**. The resulting alcohol was directly protected as the TBS ether to afford imide **31** in 75% overall yield and 55:1 dr (Scheme 6). Auxiliary cleavage and DIBAL-H reduction of **31** proceeded smoothly, providing the related aldehyde **32** in 91% overall yield. Condensation of **32** and **16** in the presence of $SnCl_4$ afforded the desired naphthylmethyl-protected phenyl thioester **29** with ~8:1 dr in 73% yield (unoptimized). Coupling of thioester **29** and amino lactam **26** was accomplished using the standard procedure (Scheme 3) as described in Scheme 7, affording amide **33** in 69% yield (unoptimized).

Fortunately, the naphthylmethyl group can be selectively removed by oxidation with DDQ, unlike the related benzyl analogue. Treatment of amide **33** with DDQ (1.5 equiv) in CH_2Cl_2/CH_3OH (4:1) at room temperature for 2 h afforded a 1:1 mixture of diol **34** and acetal **35**, the latter arising from competitive trapping of the intermediate oxonium ion by the adjacent hydroxyl group. Initial use of a higher ratio of CH_3OH or a larger amount of H_2O retards the reaction rate yet does not significantly alter the ratio of **34** and **35**. Treatment of the mixture of **34** and **35** with PPTS (5 equiv) in 1:1 CH_2Cl_2/MeOH at 45 °C for 12 h provides (+)-bengamide B (**2**),

Scheme 7



as prolonged exposure to PPTS cleaves both the acetal and the TBS ether. More efficiently, treatment of **33** with DDQ in CH_2Cl_2/CH_3OH (4:1) at room temperature for 2 h followed by the addition of PPTS (5 equiv) and sufficient CH_3OH to adjust the ratio of CH_2Cl_2 to CH_3OH to 1:1 and then warming to 45 °C for 10 h cleanly affords (+)-bengamide B (**2**) in 79% yield. Synthetic (+)-**2** was identical to an authentic sample of natural (+)-**2** by all spectroscopic criteria including optical rotation.[2b]

Acknowledgment. We thank Drs. Kenneth W. Bair, Frederick R. Kinder, and Mr. Richard W. Versace for their assistance and the Novartis Institute for Biomedical Research and the NIH (GM-30345) for generous financial support of this project.

Supporting Information Available: Experimental procedures and spectral data for key new compounds and the ^1H NMR and selected ^{13}C spectra for key intermediates and synthetic **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) NaH/2-$NpCH_2Br$; (b) NaOH/CH_3OH, then PivCl, then LiNXc/THF.