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Synthesis of Eudistomin C and E: Improved Preparation of the Indole Unit

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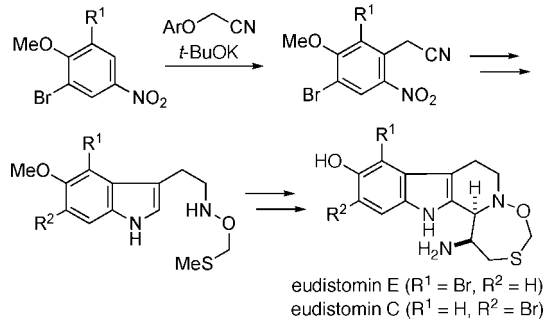
ABSTRACT



An improved synthesis of the indole unit, a key intermediate for eudistomin C, was established utilizing Makosza's indole synthesis. A concise total synthesis of eudistomin E was achieved on the basis of the improved synthesis.

Eudistomins, isolated from a Caribbean tunicate (*Eudistoma olivaceum*) by Rinehart and co-workers in 1984,[1,2] have attracted the interest of researchers because of potent antiviral, antitumor, and antimicrobial activities, as well as their unique structures including the hitherto unknown oxathiazepine ring (Figure 1). Several synthetic studies[3,4] and total syntheses[5,6] have been reported by other groups, and we have recently reported our own effort on a total synthesis of eudistomin C (**1**), featuring a stereoselective Pictet−Spengler reaction and the formation of the oxathiazepine ring by an intramolecular S_N2 reaction (Scheme 1).[7]

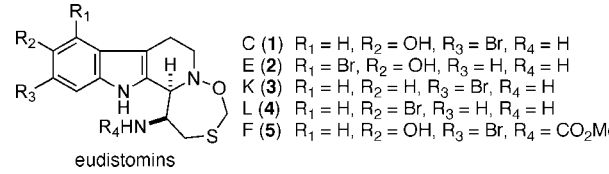


Figure 1. Structures of the eudistomins.

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(1) (a) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524. (b) Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 1526. (c) Rinehart, K. L., Jr.; Kobayashi, J.; Harbour, G. C.; Gilmore, J.; Mascal, M.; Holt, T. G.; Shield, L. S.; Lafargue, F. *J. Am. Chem. Soc.* **1987**, *109*, 3378. (d) Kobayashi, J.; Nakamura, H.; Ohizumi, Y. *Tetrahedron Lett.* **1986**, *27*, 1191.

(2) (a) Lake, R. J.; Brenman, M. M.; Blunt, J. W.; Munro, M. H. G. *Tetrahedron Lett.* **1988**, *29*, 2255. (b) Lake, R. J.; McCombs, J. D.; Blunt, J. W.; Munro, M. H. G.; Robinson, W. T. *Tetrahedron Lett.* **1988**, *29*, 4971. (c) Lake, R. J.; Blunt, J. W.; Munro, M. H. *Aust. J. Chem.* **1989**, *42*, 1201.

(3) (a) Han, S. Y.; Lakshmikantham, M. V.; Cava, M. P. *Heterocycles* **1985**, *23*, 1671. (b) Behm, H.; Beurskens, P. T.; Plate, R.; Ottenheijm, H. C. *J. Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 238. (c) Still, I. W. J.; Strautmanis, J. R. *Tetrahedron Lett.* **1989**, *30*, 1041. (d) Still, I. W. J.; Strautmanis, J. R. *Can. J. Chem.* **1990**, *68*, 1408. (e) Kirkup, M. P.; Shankar, B. B.; McCombie, S.; Ganguly, A. K.; McPhail, A. T.. *Tetrahedron Lett.* **1989**, *30*, 6809.

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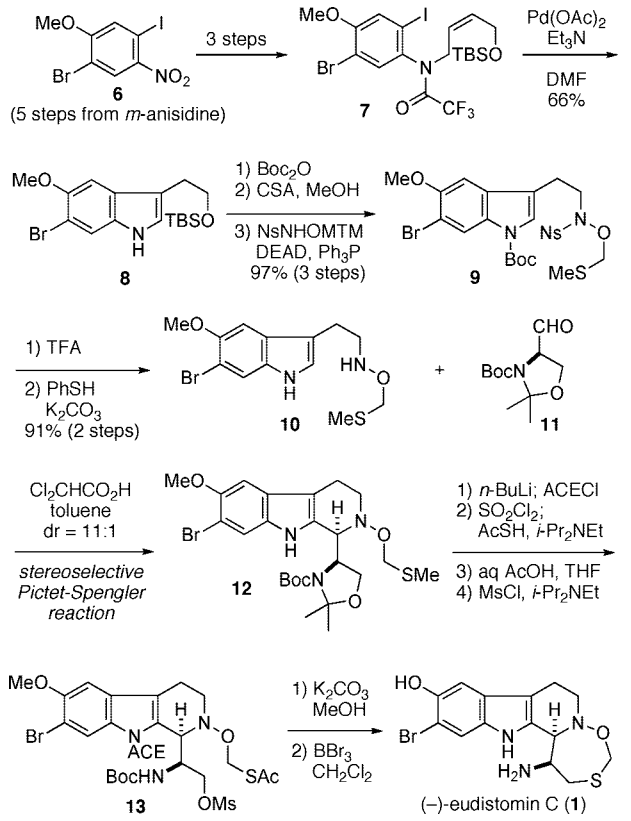
Scheme 1

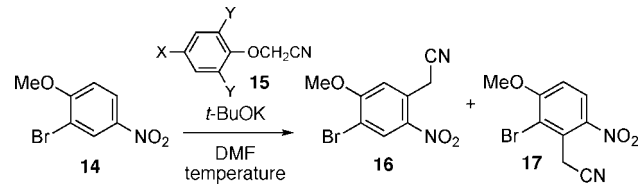


However, it was not particularly suited for a large-scale preparation of **1** and its analogs because of a multistep procedure to prepare the key intermediate **10**, including a Heck reaction to form the indole core,[8] a Mitsunobu reaction[9] to introduce the hydroxylamine moiety, and tedious protection-deprotection steps. In addition, preparation of the substituted 2-iodoanilines **6** from *m*-anisidine was not very efficient. Herein we disclose a concise route to synthesize the indole unit with the hydroxylamine moiety **10** and its application to the synthesis of eudistomin E.

Although a variety of indole syntheses have been developed, a selective synthesis of a multisubstituted indole is not necessarily an easy task. A preliminary attempt to prepare 6-bromo-5-methoxyindol-3-yl-ethanol by Fischer indole synthesis using 3-bromo-4-methoxyphenylhydrazine and dihydrofuran gave a mixture of regioisomers. In addition, regioselective halogenation of 5-methoxyindole derivative was also difficult. Although it would be possible to exclude the regiochemical problems by using the Leimgruber−Batcho indole synthesis,[10] preparation of the starting nitrotoluenes should be laborious. After intensive investigations toward an improved synthesis of the indole unit **10**, we decided to apply the Makosza's indole synthesis.[11] Their procedure involves introduction of a cyanomethyl group to the position ortho to the nitro group of nitrobenzenes, and the subsequent reduction of both nitro and cyano groups gives indoles.

According to their reported procedure, a mixture of commercially available 2-bromo-4-nitroanisole (**14**) and 4-chlorophenoxyacetonitrile (**15a**) was treated with *t*-BuOK to give a rather disappointing 2:1 mixture of the adducts (Table 1). Although the selectivity was increased when the reaction was conducted at −78 °C, it seemed less practical. In order to introduce a cyanomethyl group to the less-hindered side of the nitro group, we examined more bulky 2,6-disubstituted phenoxyacetonitriles.[12] After screening of the reagents, we found that 2,6-dichlorophenoxyacetonitrile (**15b**) gave the best result and furnished the desired product with a 6:1 regioselectivity. The resulting mixture was purified by recrystallization to afford **16** in 65% yield. Hydrogenation of the cyano and nitro groups of **16** over rhodium on carbon afforded the desired indole **18** in 52% yield with the bromo substituent intact (Scheme 2).

Table 1. Regioselectivity of the Introduction of a Cyanomethyl Group



reagent	X	Y	temp (°C)	ratio (**16**:**17**)[a]	yield (%)[b]
15a	Cl	H	0	2:1	95
15a	Cl	H	−78	10:1	89
15b	H	Cl	0	6:1	86
15c	Cl	Cl	0	5:1	81
15d	H	Br	0	5:1	84
15e	H	Me	0	3:1	51

[a] Ratio was determined by ^{1}H NMR. [b] Isolated yields.

With the indole core in hand, we then introduced the side chain with the hydroxylamine moiety (Scheme 2). Indole **18** was subjected to a Mannich reaction to give gramine **19**, which after neutralization with an aqueous sodium hydroxide solution was treated with sodium cyanide to afford 3-in-

(5) (a) For (−)-eudistomin L and (−)-debromoeudistomin L, see: Nakagawa, M.; Liu, J.-J.; Hino, T. *J. Am. Chem. Soc.* **1989**, *111*, 2721. For (−)-eudistomins, C, E, F, K, and L, see: (b) Nakagawa, M.; Liu, J.-J.; Hino, T.; Tsuruoka, A.; Harada, N.; Ariga, M.; Asada, Y. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3477. (c) Liu, J.-J.; Hino, T.; Tsuruoka, A.; Harada, N.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3487. For (−)-eudistomin F, see: (d) Liu, J.-J.; Nakagawa, M.; Harada, N.; Tsuruoka, A.; Hasegawa, A.; Ma, J.; Hino, T. *Heterocycles* **1990**, *31*, 229.

(6) For (−)-debromoeudistomin L, see: Hermkens, P. H. H.; van Maarseveen, J. H.; Ottenheijm, H. C. J.; Kruse, C. G.; Scheeren, H. W. *J. Org. Chem.* **1990**, *55*, 3998.

(7) (a) Yamashita, T.; Kawai, N.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2005**, *127*, 15038. (b) Yamashita, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2003**, 738.

(8) Macor, J. E.; Ogilvie, R. J.; Wythes, M. J. *Tetrahedron Lett.* **1996**, *37*, 4289.

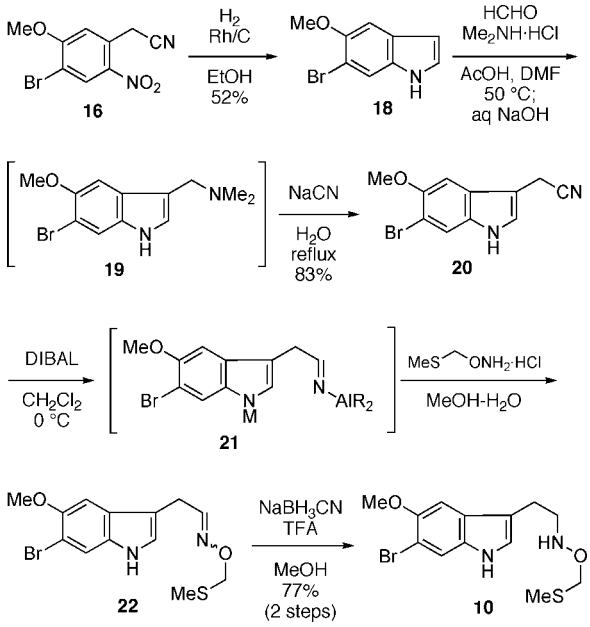
(9) Mitsunobu, O. *Synthesis* **1981**, 1.

(10) Batcho, A. D.; Leimgruber, W. *Organic Synthesis*; Wiley: New York, 1990; *Collect. Vol. VII*; p 34.

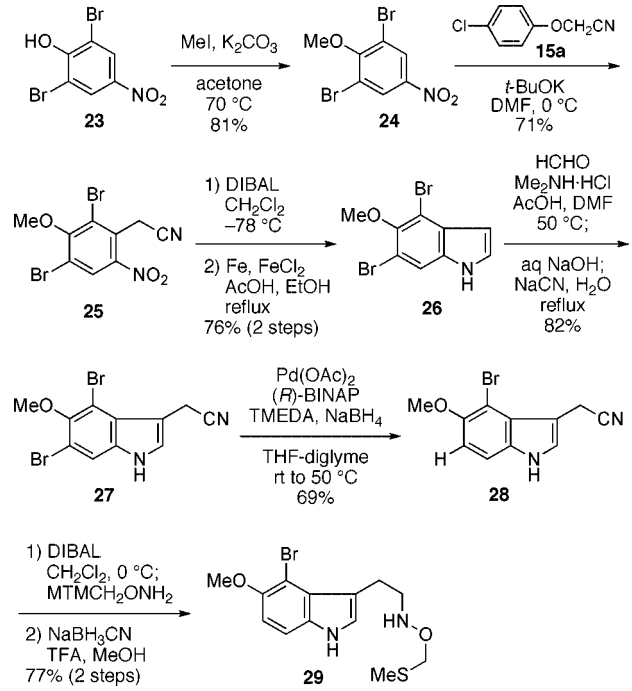
(11) Makosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1988**, 203.

(12) For halogenation of the nitrobenzenes to bias the regiochemistry of the Makosza's indole synthesis, see: Lerman, L.; Weinstock-Rosin, M.; Nudelman, A. *Synthesis* **2004**, 3043.

Scheme 2



Scheme 3



doleacetonitrile **20**.[13] After reduction of the cyano group of **20** with DIBAL to give imine **21**, *O*-MTM hydroxylamine hydrochloride[14] in methanol−water was added to the reaction mixture to furnish oxime ether **22** in good yield without isolating the labile indoleacetaldehyde. Reduction of oxime ether **22** with sodium cyanoborohydride afforded the requisite indole unit **10** with the hydroxylamine moiety. Thus, the novel synthetic route produced **10** from a commercially available substrate in five steps and 22% overall yield.[15]

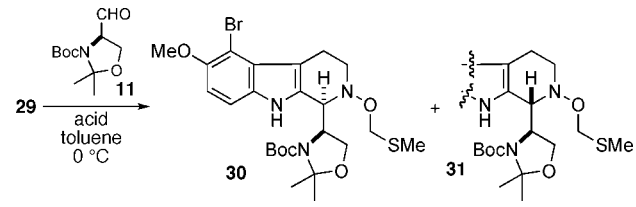
Having established an efficient synthetic route to **10**, we next focused on application to the synthesis of eudistomin E (**2**), which has a bromo group at the 5-position. Although the minor isomer **17** in the reaction of Makosza's indole synthesis (Table 1) was a suitable substrate, isolation from the mixture of regioisomers was a tedious task.[16] Therefore, we opted to prepare the requisite indole unit by cyanomethylation of symmetrical 2,6-bromo-4-nitroanisole and removal of one of two bromo groups using the hydrodebromination developed by Buchwald and co-workers[17] after formation of indole ring.

The synthesis commenced with the methylation of commercially available 2,6-dibromo-4-nitrophenol (**23**). The cyanomethyl group was introduced to **24** using 4-chlorophenoxyacetonitrile (**15a**) to furnish **25** in 71% yield. Because the reductive cyclization by catalytic hydrogenation of **25** was accompanied by partial debromination, the cyano and nitro groups were sequentially reduced to give indole **26**.

After introduction of a cyanomethyl group via Mannich reaction, a selective hydrodebromination was performed according to Buchwald's procedure. That is, **27** was treated with sodium borohydride in the presence of a palladium catalyst. The reaction occurred preferentially at the less hindered bromo group to furnish **28** in 69% yield. The cyano group was converted into the hydroxylamine moiety in the same manner as shown above to give **29** in good yield.

Having synthesized the requisite indole unit **29**, we next needed to optimize the crucial Pictet−Spengler reaction of **29** with Garner aldehyde (**11**).[18] The conditions using

Table 2. Optimization of the Pictet−Spengler Reaction



acid	temp (°C)	ratio (**30**:**31**)	yield of **30** (%)
Cl_2CHCO_2H	0 to rt	1.0:2.7[a]	26
$BF_3{\cdot}OEt_2$	0	1.0:1.0[b]	
$ZnCl_2$	0	1.0:1.0[b]	
$SnCl_4$	0	1.6:1.0[b]	
$AlCl_3$	0	1.7:1.0[b]	
$TiCl_4$	0	1.7:1.0[b]	
$BrCH_2CO_2H$	0 to rt	2.3:1.0[a]	63

[a] Ratio was determined on the basis of the isolated yields. [b] Ratio was determined by ^1H NMR.

(13) (a) Somei, M.; Kizu, K.; Kunimoto, M.; Yamada, F. *Chem. Pharm. Bull.* **1985**, *33*, 3696. (b) Lisas, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918.

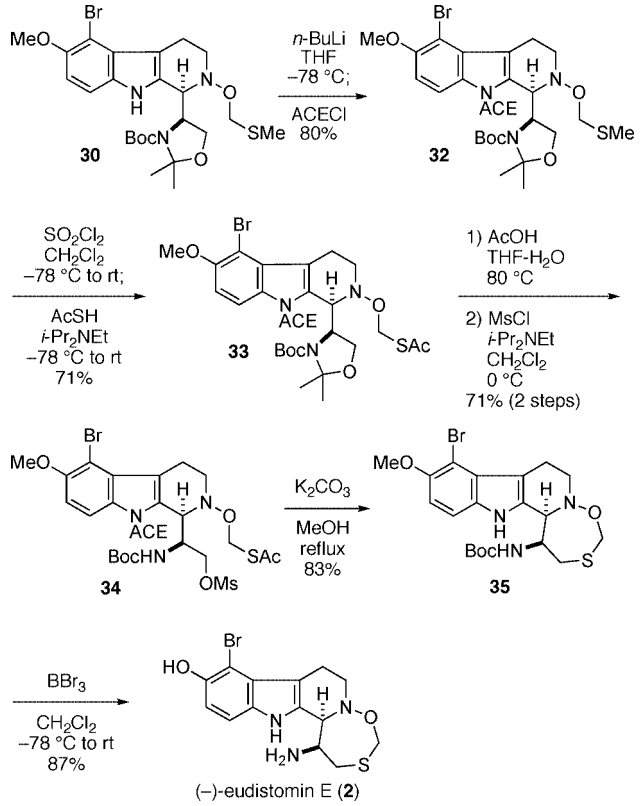
(14) Vlattas, I.; Vecchia, L. D.; Fitt, J. J. *J. Org. Chem.* **1973**, *38*, 3749.

(15) Our previous syntheis gave **10** from *m*-anisidine in fourteen steps and 7.4% overall yield.

(16) Althought the production of **17** was increased when the reaction was performed at 50 °C, the selectivity was 3:2 at most.

(17) Chae, J.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 3336.

Scheme 4



dichloroacetic acid in toluene, which was optimal for the synthesis of eudistomin C (desired:undesired = 11:1),[7a] afforded the undesired isomer **31** as the major product (Table 2). Using trifluoroacetic acid resulted in lower diastereoselectivity. When acetic acid was employed, the selectivity was improved, but the substrate was not consumed because of its low acidity. After extensive screening of acids including Lewis acids, we found that bromoacetic acid afforded the desired isomer **30** in 63% isolated yield.

The Pictet−Spengler reaction product was then transformed into eudistomin E according to the procedure developed in our laboratory (Scheme 4).[7a] After protection of indole NH of **30** with an α-chloroethoxycarbonyl (ACE) group,[19] the MTM group of **32** was converted into a chloromethyl group by treatment with sulfuryl chloride.[20] The resulting chloromethyl ether was immediately reacted with thioacetic acid in the presence of Hunig's base to furnish thiol acetate **33**. Removal of the acetonide and subsequent mesylation of the resulting alcohol afforded mesylate **34**.Methanolysis of the thiol acetate induced a subsequent intramolecular S_N2 reaction and concomitant removal of ACE group to furnish oxathiazepine **35** in 89% yield.[21] Finally, the methyl ether and Boc group were cleaved to afford eudistomin E (**2**). The spectroscopic data of eudistomin E obtained are consistent with those reported in the literature.[1a]

In conclusion, we have developed a concise synthetic route to the key indole intermediate for the synthesis of eudistomins C. Moreover, by modification of this improved route, we have achieved the total synthesis of eudistomin E. This novel route to the key indole unit should be applicable to the synthesis of a variety of derivatives starting from readily available nitrobenzenes. The syntheses of a broad range of eudistomin derivatives are currently underway and will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Garner, P.; Park, J. M. *Org. Synth.* **1992**, *70*, 18. (b) Dondoni, A.; Perrone, D. *Org. Synth.* **1999**, *77*, 64.

(19) Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. *J. Org. Chem.* **1984**, *49*, 2081.

(20) (a) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762. (b) Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125.

(21) Alternatively, compound **35** was synthesized as follows: According to the synthetic scheme described above, dibromoindole **27** was converted into a eudistomin derivative **36** via a $TiCl_4$-mediated Pictet-Spengler reaction with **11**. The Buchwald hydrodebromination reaction of **36** gave **35** in only 21% yield. Detailed procedures are provided in Supporting Information.