Pergamon

Tetrahedron Letters, Vol. 35, No. 16, pp. 2573-2576, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0406-N

Total Synthesis of an Antitumor Antibiotic, (±)-Duocarmycin SA

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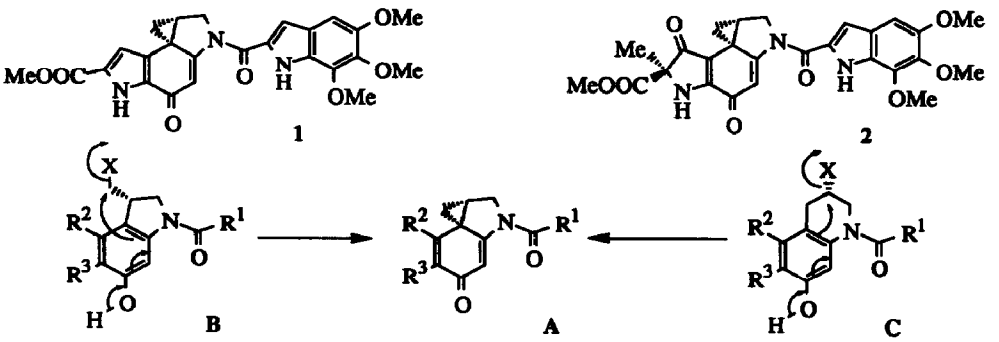
Abstract: *A 12-step total synthesis of (±)-duocarmycin SA (1) was achieved from a readily available pyrrole 3 by way of 7, 10 / 11, 14 and 18, using a $SnCl_2$-mediated reaction of a singlet oxygen adduct 6 with 5, as well as the Heck and Mitsunobu reactions on 9 and 16 as key steps.*

Duocarmycin SA (1) is a potent antitumor antibiotic, isolated from a culture broth of the *Streptomyces* species.[1] In common with other structurally related duocarmycins,[2] pyrindamycins,[3] and CC-1065,[4] 1 has a partial structure A of *N*-acylcyclopropanoindolinone which is the essential, biologically active site for the alkylation of DNA.[5] Specifically, only 1 has a methyl α-pyrrolecarboxylate unit at the R^2 and R^3 positions, and this unit is incorporated with the above cyclopropanoindolinone moiety. These structural features contribute to a pronounced stability of duocarmycin SA (1) (meaning stable A) relative to duocarmycin A (2), and benefits in planning a synthetic approach to 1, since we already have vast experience with indole synthesis starting from a pyrrole derivative.[6] Boger and a co-worker reported the first synthesis of 1 in 1992.[7]

Our synthesis plan definitely differs from most previously reported syntheses of 1,[7] 2,[8] CC-1065,[9] and its synthetic analogues,[10] where the essential structural unit A was constructed from an easily conceivable precursor B. By contrast, we envisioned the formation of A from a tetrahydroquinolinol derivative C carrying a hetero-atom X.[11] In the actual synthesis, this process proceeded with exceptional ease employing the Mitsunobu reaction[12] on a compound having a partial structure C, where X was simply a hydroxyl group, bringing us the



successful accomplishment of a second synthesis of (±)-**1**.

Construction of a tricyclic structural core **10** / **11**, for the further derivation to a hydroxyindole derivative **14**, was substantiated by an intramolecular version of the Heck reaction[13] on the precursor molecule **9**. For that purpose, the bromoacetylpyrrole derivative **4** was prepared by Friedel-Crafts acylation on **3**,[14] and converted into its *t*-butyldimethylsilyl enol ether **5** in a high yield. This compound **5** was condensed with a singlet oxygen adduct **6** of 1-benzyloxycarbonyl-1,2-dihydropyridine in the presence of $SnCl_2$ to yield trans **7** and cis **8** derivatives, the former being produced in a predominant ratio.[15] The Pd-catalyzed intramolecular cyclization reaction on **7**, **8** and their *O*-methoxymethyl, benzyl and *t*-butyldimethylsilyl derivatives was investigated under a variety of reaction conditions. All trans compounds, *i.e.* **7** and its *O*-derivatives, were found to afford the corresponding tricyclic compounds in fairly good yields. Among these, the best result was obtained by heating an acetonitrile solution of the benzyl ether **9**, prepared from **7** using benzyl trichloroacetimidate and CF_3SO_3H,[16] with $Pd(OAc)_2$ (5 mol %) and P(*o*-tolyl)$_3$ (13 mol %) in the presence of Et_3N (1 mol equiv) under an Ar atmosphere at 110°C for 26 h in a sealed tube to produce **10** and **11** totally in greater than 90% yield.[17] Contrary to the successful Heck reaction with the trans compounds, neither **8** nor its *O*-derivatives gave any cyclization products under similar Pd conditions, except for the recovery of the starting materials in modest to moderate yields.[17] Therefore, the useless compound **8** was changed to **7** using the Mitsunobu reaction,[12] followed by methanolysis in a good overall yield.

Both **10** and **11** were transformed into the same dimethyl acetal **12** under selected conditions employing $MeOSiMe_3$ and Me_3SiOTf in good respective yields.[18] The next aromatization process, from **12** to **14**, was performed by two successive operations by way of an α-phenylselenyl ketone **13**. Thus, **12** was treated with Me_3SiOTf[19] in the presence of Et_3N, and the silyl enol ether obtained here was phenylselenated with PhSeCl in the presence of *n*-Bu_4NF[20] to afford **13**. Oxidative elimination of the PhSe group was carried out by treatment with *m*-chloroperbenzoic acid in THF, and the requisite hydroxyindole **14** was obtained in a good overall yield, accompanied by the formation of a by-product **15**. Reductive removal of the PhSe group from the latter compound was made possible by treatment with nickel boride,[21] prepared *in situ* from $NiCl_2 \cdot 6H_2O$ and $NaBH_4$, to give **14** in a very good yield. The dimethyl acetal group of **14** was removed to afford an unstable ketone derivative, which was further reduced with $NaBH_4$ without any purification, and diol **16** was produced as a crystalline compound in a good overall yield.

Now the synthesis arrived at the final stage for the formation of the cyclopropane ring. Fortunately the above synthetic pathway directly afforded the diol derivative **16**, so that the Mitsunobu reaction could be tried for the dehydrative cyclopropanoindolinone construction according to the scheme **C** → **A**. Rather than using the usual reagent DEAD, use of 1,1'-(azodicarbonyl)dipiperidine[22] gave a satisfactory result, providing **17** in 88% yield. Since the Cbz group in **17** was situated at the N atom involved in a vinylogous amide function, it was readily cleaved by treatment with K_2CO_3 in MeOH at room temperature to give an *N*-unprotected compound **18** in an excellent yield. This compound **18** was condensed with an activated form **19** of 5,6,7-trimethoxyindole-2-carboxylic acid in the presence of NaH. Thus, the total synthesis of (±)-duocarmycin SA (**1**) was complete in 12 steps starting from the readily available compound **3**. Identity of the synthetic material with the natural product was confirmed by comparison of their IR ($CHCl_3$) and ^1H and ^{13}C NMR spectra. Further study aimed at the chiral synthesis of natural (+)-duocarmycin SA is now in progress.

ACKNOWLEDGMENT

Authors' thanks are due to Dr. I. Takahashi of Kyowa Hakko Kogyo Co., Ltd., for the kindly supply of copies of IR and ^{1}H NMR spectra of duocarmycin SA. This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, which is acknowledged with appreciation.

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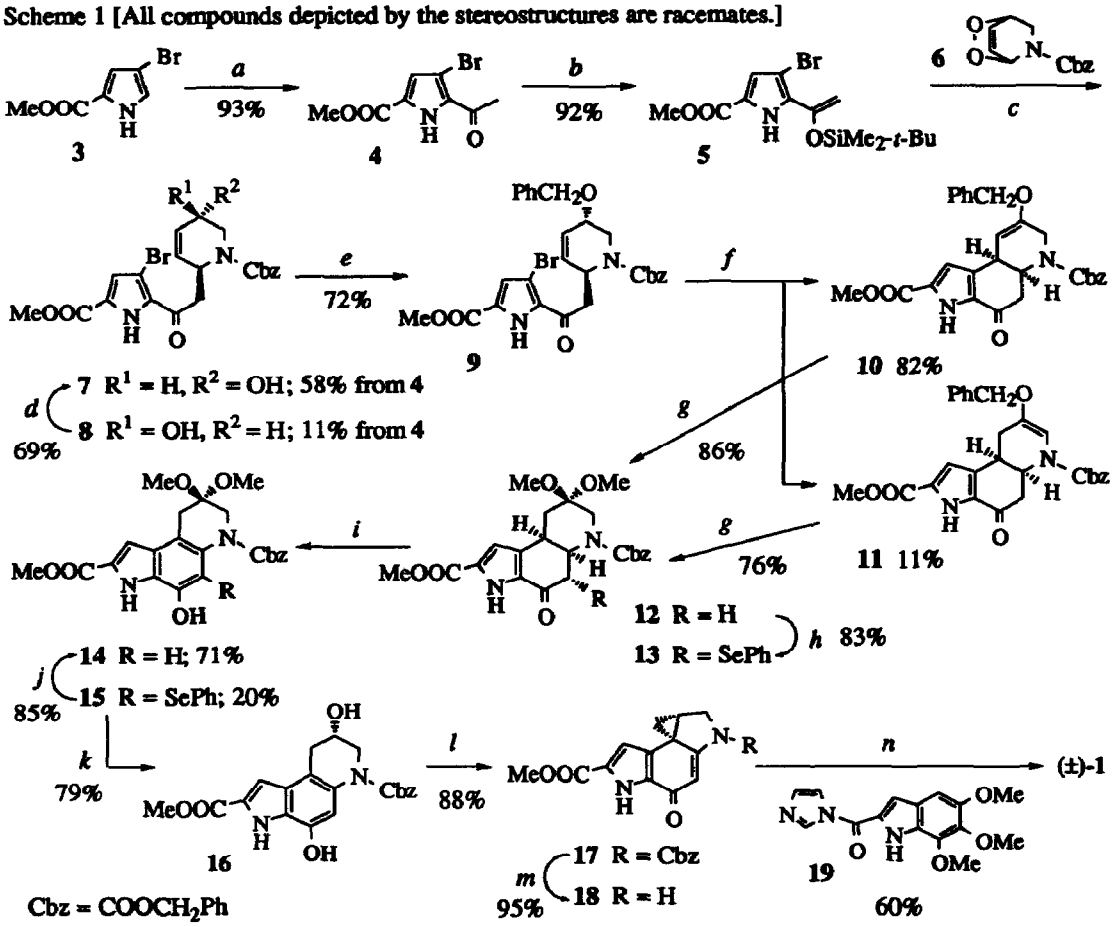
Scheme 1 [All compounds depicted by the stereostructures are racemates.]



a: Ac_2O, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0°C. *b*: *tert*-$BuMe_2SiOTf$, Et_3N, CH_2Cl_2, 0°C. *c*: **6**, $SnCl_2$, EtOAc, –70° → 0°C. *d*: i) HOAc, DEAD, Ph_3P, THF, 0° → 22°C, 74%; ii) K_2CO_3, MeOH, 19°C, 93%. *e*: $Cl_3CC(=NH)OCH_2Ph$, CF_3SO_3H, cyclohexane-CH_2Cl_2, 0° → 20°C. *f*: $Pd(OAc)_2$, P(*o*-Tol)$_3$, Et_3N, MeCN, 110°C. *g*: $MeOSiMe_3$, Me_3SiOTf, CH_2Cl_2, –20° → 0°C. *h*: i) Me_3SiOTf, Et_3N, CH_2Cl_2, 0° → 22°C; ii) PhSeCl, *n*-Bu_4NF, THF, 0° → 22°C. *i*: *m*CPBA, THF, –20°C. *j*: $NaBH_4$, $NiCl_2{\cdot}6H_2O$, THF-MeOH, 0°C. *k*: i) *p*-TsOH·H_2O, acetone, 24°C ii) $NaBH_4$, MeOH, –20°C. *l*: *N*-piperidyl-CO-N=N-CO-*N*-piperidyl, *n*-Bu_3P, THF, 0° → 26°C. *m*: K_2CO_3, MeOH, 23°C. *n*: i) NaH, DMF-THF; ii) **19**, 0°C.

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(*Received in Japan* 15 *November* 1993; *accepted* 10 *January* 1994)