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Synthesis of Both Enantiomers of Dynemicin A Model Compound. New Remote Asymmetric Induction in Acetylide Addition into Quinoline Nucleus as Key Step

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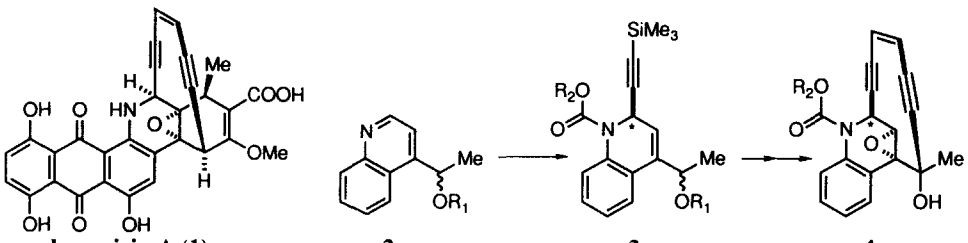
Abstract: A new and highly selective 1,4-asymmetric induction in the addition of magnesium acetylide into quinoline nucleus was developed. By using this reaction, both enantiomers of dynemicin A model compound were synthesized from chiral alcohol which was prepared by lipase catalyzed resolution.

Dynemicin A **1**,[1] a novel hybrid antitumor antibiotic substance having anthraquinone and cyclic enediyne structure, has been focused as other enediyne antibiotics such as neocarzinostatin-chromophore, calicheamicin, esperamicin, *etc*.[2] These antibiotics show extraordinary potent biological activities responsible for DNA-cleavage *via* Bergman cycloaromatization. Recently, however, some enediyne compounds related to dynemicin A show different type of action mechanism.[3] In the connection with our studies on dynemicin A,[4] we have synthesized the racemic model compound **4** (**Scheme 1**).[5] In order to estimate the difference of biological activities between both enantiomers and to obtain the information about absolute stereochemistry of dynemicin A which has not been determined yet,[6] we decided to synthesize the model compound as a chiral form.[7] In this letter, we describe the syntheses of both enantiomers of dynemicin A model compound **4**.



dynemicin A (1) **2** **3** **4**

Scheme 1

Outline of our synthesis of racemic **4** is shown in **Scheme 1**, where 3 stereogenic centers in **4** were induced from the asymmetric center (*) of propargylic position. We planned stereoselective introduction of acetylene group induced by the stereogenic center at side chain of **2**. In our previous report on the synthesis of racemic **4**, magnesium acetylide was introduced into quinoline **2** (R_1 = TBDMS) with ethyl chloroformate at 0 °C, whose diastereoselectivity was about 1:2 (by ^1H NMR analysis).[5] This selectivity may be attributed to the preferential rotamer shown in **Figure 1**. If acetylide anion might attack from the less hindered face

(opposite face to OR_1), the larger protective group of R_1 would give the higher selectivity. Results of the selectivity under different size of R_1 and different type of R_2 at different temperatures using racemic **2** are shown in **Table 1**. Combination in entry 6 comprising TBDPS as protective group in the substrate, phenyl carbamate and low reaction temperature (-78 °C) gave the highest selectivity (1:13 by ^1H NMR analysis). Determination of the relative stereochemistry is described later.

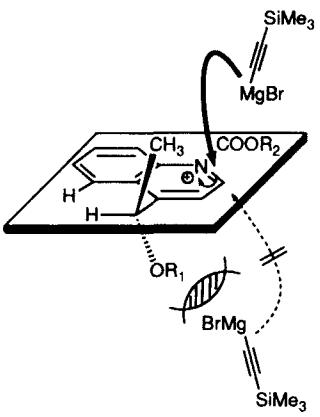


Figure 1

Scheme 2

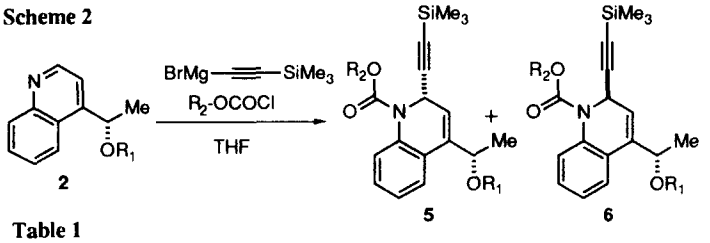
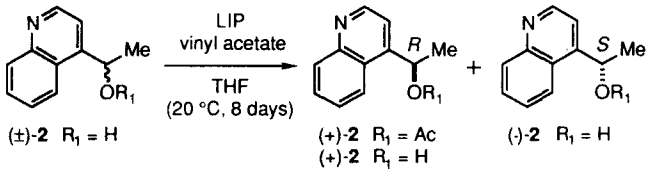


Table 1

entry	R_1	R_2	temp (°C)	yield (%)	selectivity (**5** : **6**)
1	MOM	Me	0	65	1 : 1.1
2	TES	Me	0	63	1 : 1.5
3	TBDPS	Me	0	85	1 : 2.3
4	TBDPS	Ph	0	100	1 : 4.9
5	TBDPS	Ph	-20	100	1 : 5.6
6	TBDPS	Ph	-78	87	1 : 13

The remaining problem was preparation of the chiral starting alcohol **2** for **Scheme 4**. Heathcock's report on preparative scale resolution of 1-(1'-naphthyl)ethanol by lipase[8] prompted us to use lipase in an organic medium to solve this problem. After screening some commercially available lipases,[9] we found that LIP (immobilized lipase from TOYOBO) acetylated one of the enantiomers to give (+)-**2** (R_1 = Ac) in high optical purity (51 % yield, 96 % ee,[10] $[\alpha]_D$ +39.0 (*c* 1.00, $CHCl_3$)) and the residual alcohol (-)-**2** (R_1 = H) was also obtained in 48 % yield (95 % ee, $[\alpha]_D$ -86.6 (*c* 1.00, $CHCl_3$)) (**Scheme 3**). (+)-**2** was determined to be (*R*) absolute configuration by advanced Mosher's method (**Figure 2**).[11]



Scheme 3

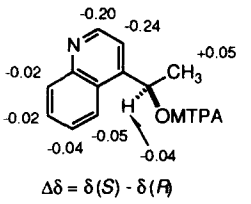
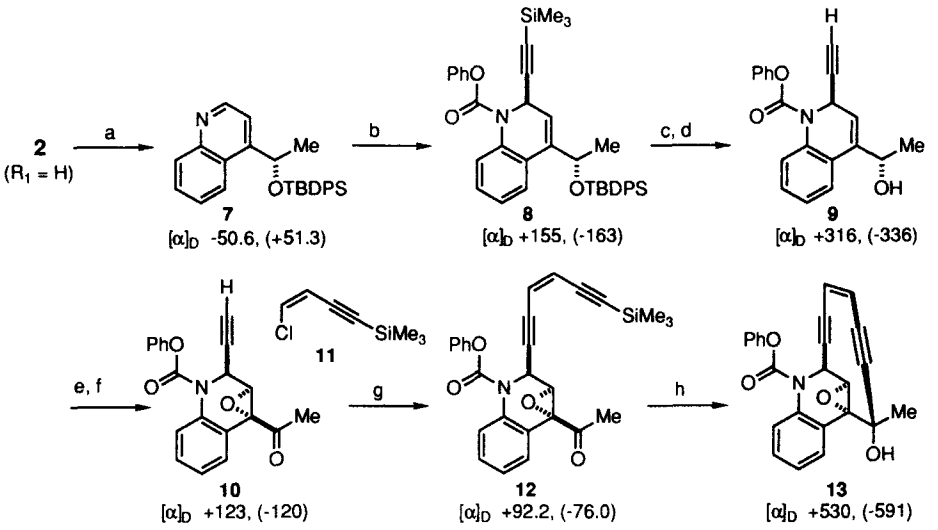


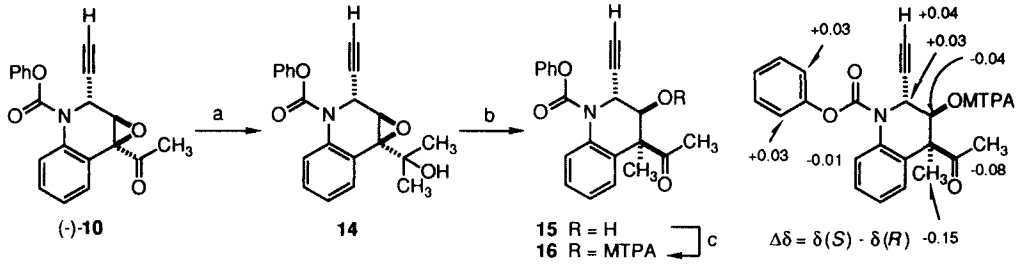
Figure 2

Chiral model compound (+)-**13** was synthesized from (*S*)-**2** (R_1 = H) as shown in **Scheme 4** according to the racemic synthesis of **4**.[12] The other enantiomer (-)-**13** was synthesized from (*R*)-**2** (R_1 = H) in a similar manner. The values of optical rotation are shown below the structures in **Scheme 4**, while the values in parentheses are those of the optical rotation of the corresponding opposite enantiomer.



Scheme 4. Reagents and conditions: (a) TBDPS-Cl, imid. / DMF, 70 °C, 19 h, 92 % (86 %); (b) see: entry 6 in Table 1, 71 % (68 %); (c) TBAF / THF-MeOH, 0 °C, 25 min; (d) $TsOH{\cdot}H_2O$ / MeOH, reflux, 11.5 h, 84 % (84 %) in 2 steps; (e) MCPBA, Na_2HPO_4 / CH_2Cl_2, 0 °C, 2 h, 89 % (100 %); (f) $SO_3{\cdot}Py$, Et_3N / DMSO-CH_2Cl_2, 0 °C-rt, 78 % (75 %); (g) **11**, $Pd_2[dba]_3{\cdot}CHCl_3$, Ph_3P, CuI, *n*-$BuNH_2$ / benzene, rt, 2 h, 64 % (57 %); (h) CsF, 18-crown-6 / THF, rt, 4 h, 12 % (12 %).

The absolute stereochemistry of **13** was determined through **10** by chemical transformation as illustrated in **Scheme 5**.[12] Addition of methylmagnesium bromide to ketone (-)-**10** gave *tert*-alcohol **14**. Semi-pinacol rearrangement[13] induced by $BF_3{\cdot}OEt_2$ gave **15**[14] whose absolute stereochemistry was determined by advanced Mosher's method[11] (**Figure 3**). Since the *anti* relationship between acetylene and epoxide in **10** had been known,[5] the absolute stereochemistry of (+)-**10** and (+)-**13** were determined as shown in **Scheme 4**.



Scheme 5. Reagents and conditions: (a) MeMgBr / THF, 0 °C, quant.; (b) $BF_3{\cdot}OEt_2$ / CH_2Cl_2, -78 °C, 52 %; (c) (*S*)-or (*R*)-MTPA-Cl, DMAP, Et_3N.

Figure 3

DNA-cleaving activities of both synthesized enantiomers (+)-**13** and (-)-**13** were indistinguishable by means of the assay using the topological change of ϕX174 DNA.[5b] Argument of the absolute stereochemistry of (+)-**13** is of much interest in comparing the proposed absolute stereostructure[6] of dynemicin A ($[\alpha]_D$ +270)[1] and of (+)-model compound synthesized by K. C. Nicolaou's group.[7] Studies on *in vitro* biological activity of our compounds are now in progress.

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9. The difficulty in application of the alcohol (±)-**2** (R_1 = H) to enzyme reaction was the low solubility of (±)-**2** (R_1 = H) to organic solvents such as heptane, toluene, *etc.* Although the solubility to THF was high enough, the enzyme activity of LIP was lost during the reaction.
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12. All intermediates were characterized by IR, ^{1}H and ^{13}C NMR, HRMS and/or elemental analysis.
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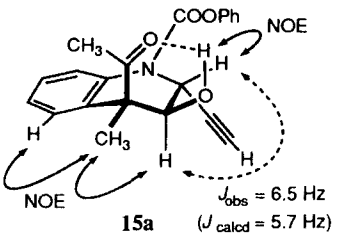
14. Conformation of **15** was determined as shown in **15a** by ^{1}H NMR and molecular mechanics calculations using MacroModel (MM2). We are grateful to Prof. W. C. Still for providing a copy of this program. **MacroModel** V4.0; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440-467.



15a

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