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An Optically Active Allene Macrodiolide: A Versatile Key Intermediate Leading to (-)-Pyrenophorin and (+)-Dibenzomacrodiolides

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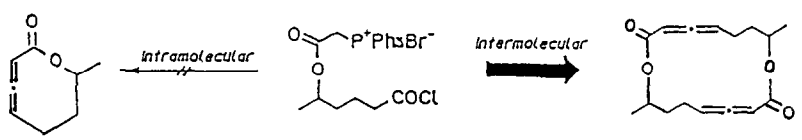
Abstract: The optically active allene macrodiolides via the macrocyclization of allenic ester provide a simple route to (-)-pyrenophorin and (+)-dibenzomacrodiolide, respectively.

Among the various functional groups, allenic ester is known for its high reactivity and unique structure.[1] As a part of our investigation of allenic ester as building blocks[2], it seems that the allenic ester syntheses[3] for macrocyclization might offer some advantages, since this type of reaction such as Wittig-Horner reaction was shown to be effective for macrocyclization.[4] If we use this type of reaction for macrocyclization, intramolecular cyclization of **1** would produce monomeric 8-membered allene lactone (**2**) which is thought to be most difficult to cyclize.[5] Thus, intermolecular cyclization would be preferred for the mode of macrocyclization leading to 16-membered allene dilactone (**3**)



2 1 3

Moreover, if we use allenic ester as a tool for functionalization, the allene dilactone (**3**) would easily be converted not only to natural (-)-pyrenophorin (**4**) but also to unnaturally novel dibenzomacrodiolide (**5**) with potential pharmacological activity.[6]

First of all, we examined the macrocyclization of various allenic esters. tert-Butyl 5-bromoacetoxyhexanoate **7a** was prepared from **6a**[7] by the sequence of esterification (tert-butyl alcohol/DCC/4-PPY)[8], reduction ($NaBH_4$) and acylation ($BrCH_2COBr$/ $KHCO_3$). Conversion of **7a** to the acid chloride **8a** was achieved by the following sequence; 1) PPh_3, benzene, r.t., overnight ; 2) TFA, neat, 10 min.; 3) $(COCl)_2$, benzene, r.t., 3 h. Thus, requisite acid chloride **8a** was treated with 6.4 equiv. of triethylamine, and separation by silica gel chromatography gave allene dilactone **3a** along with some trimer and tetramer (Scheme I). The results are summarized in

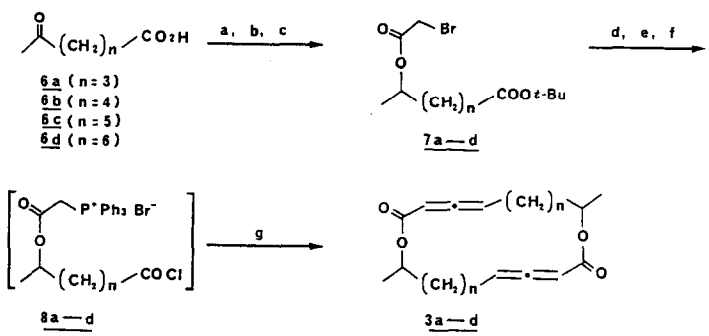
Table I.

Table I. Conditions for Macrocyclization

entry	conditions (temp., time)	concentration (mmol/ml)	yield (%)	ratio of dimer/trimer
1	r.t., overnight	4.9×10^{-3}	0	-----
2	r.t., overnight	9.3×10^{-3}	5	dimer only
3	r.t., 3h	3.57×10^{-2}	23	1:0.8[b]
4	r.t., 3h	5.00×10^{-2}	18	1:0.8
5	r.t., 2h	1.00×10^{-1}	6	ca.1:1
6	r.t., 20h[a]	3.46×10^{-1}	6	ca.1:1[c]

a; Syringe pump addition over 18 h. b; Tetramer was isolated in 8% yield.
c; Tetramer was isolated in 0.8% yield.

Scheme I



Reagents and conditions : a) t-BuOH/DCC/4-PPY, CH_2Cl_2, room temp., 24 h or t-BuOAc/$HClO_4$, room temp., 24 h ; b) $NaBH_4$, EtOH, 0°C, 1.5 h ; c) $BrCH_2COBr/KHCO_3$, benzene, room temp., 2 h ; d) PPh_3, benzene, room temp., over night ; e) CF_3COOH, neat, room temp., 10 min. ; f) $(COCl)_2$, benzene, room temp., 2 h ; g) Et_3N, CH_2Cl_2

It should be noted that the ratio of dimer/trimer became larger as the concentration goes from high to low. The optimized yields for cyclization indicate that moderately dilute conditions are necessary. We briefly examined the possibility of intramolecular cyclization from 8- to 11-membered ring (n=3-6),[9,10] but none of the chain length could cyclize intramolecularly under the conditions obtained above (Table II).

Table II. Effect of Chain Length for Macrocyclization

chain length (n)	conditions (temp., time)	concentration (mmol/ml)	yield(%)[a] dimer	trimer	tetramer
3	r.t., 3h	3.57×10^{-2}	23	18	8
3	r.t., 3h	5.00×10^{-2}	18	14	trace
4	r.t., 3h	2.63×10^{-2}	12	---[b]	6
4	r.t., overnight	4.60×10^{-2}	13	---[b]	2
5	r.t., 3h	4.60×10^{-2}	10	6	3
6	r.t., 3h	4.58×10^{-2}	21	---[b]	---[c]

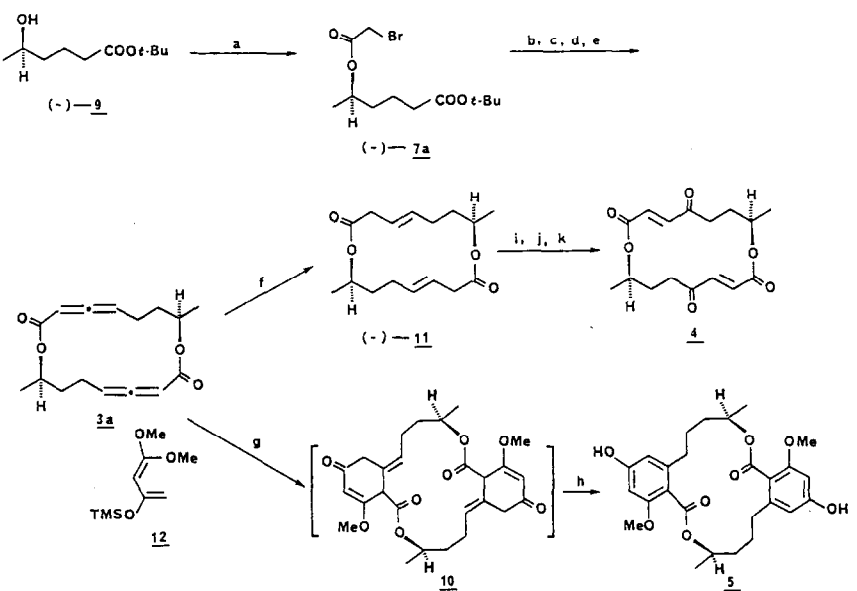
a ; Isolated yield based on bromoacetate (10a-d). b; Trimer was not detected.
c ; Tetramer was not detected.

Now, the stage was set for the synthesis of (-)-pyrenophorin (**4**) and optically active dibenzomacrodiolide (**5**). The key intermediate **(-)-9** was easily synthesized from commercially available poly-β-hydroxybutyric acid

(PHB)[11] by the sequence of Seebach's procedure[12], and the allenic ester cyclodimerization was carried out as described above. They were obtained as mixtures of two diastereomers ((-)- and (+)-**3a**) and can be separated by silica gel chromatography. They are almost identical except for specific rotation (the less polar fraction (-)-**3a**: $[\alpha]_D^{25}$ -197°, (c 0.49, $CHCl_3$); the more polar fraction (+)-**3a**: $[\alpha]_D^{26}$ +89°, (c 0.54, $CHCl_3$)). The structure of each separated isomer could not be determined at present, but they were reduced by Saegusa's method[13] smoothly to give the same product (-)-**11** [$[\alpha]_D^{21}$ -54.14°, (c 0.41, $CHCl_3$)] in total 70% yield. Thus, two isomers were diastereomers of allenic parts. By this, we accomplished formal total synthesis of (-)-pyrenophorin (**4**) which has been previously synthesized from (-)-**11** by the sequence of epoxidation and epoxide opening followed by Jones oxidation according to the procedure of Seebach et al.[14]

On the other hand, Diels-Alder reaction of the allene dilactones (-)- and (+)-**3a** with diene such as the siloxy diene **12**[15] in xylene (sealed tube, 150°C, 8 h) followed by aromatization (p-TsOH, benzene, reflux, 1 h) afforded a novel dibenzomacrodiolide (**5**), mp. 68-72°C [$[\alpha]_D^{30}$ +8.25°(±1.5) (c 0.59, $CHCl_3$), FD-MS m/z= 473 (M^++1)] in moderate yield.

Scheme II



Reagents and conditions : a) $BrCH_2COBr/KHCO_3$, benzene, room temp., 2 h ; b) PPh_3, benzene, room temp., over night ; c) CF_3COOH, neat, room temp., 10 min.; d) $(COCl)_2$, benzene, room temp., 2 h ; e) Et_3N, CH_2Cl_2, room temp., 3 h ; f) DIBAH/MeCu, THF:HMPA=5:1, -50°C, 3 h ; g) 12, xylene, sealed tube, 150°C, 8 h; h) p-TsOH, benzene, reflux, 1 h ; i) m-CPBA, $CHCl_3$, 0°C, 10 h ; j) LDA, THF, -78°C, 1 h ; k) Jones oxidation, acetone, room temp., 20 min.

The use of this reaction in the synthesis of optically active other membered macrodiolides and further development of the methodology are currently under way.

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