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Synthesis of the C(1)–C(8) segment of (+)-acutiphycin

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Abstract—The synthesis of the pyran segment of (+)-acutiphycin was achieved using an intramolecular Lewis acid-catalyzed reaction between a silyl enol ether and an *ortho* ester.

In 1984, Moore and co-workers reported the isolation and characterization of two novel macrolides produced by the blue-green alga *Osillatoria acutissima*, (+)-acutiphycin (**1**) and (+)-*trans*-20,21-didehydroacutiphycin (**2**) (Fig. 1).[1]

The crude extract of *O. acutissima* exhibited significant antineoplastic activity in vivo against murine Lewis lung carcinoma and was cytotoxic against KB and NIH/3T3 cells. This biological activity is due to the presence of **1** and **2** in the extract.[1] Since then, the blue-green alga has stopped producing these macrolides, making a synthetic approach to these natural products even more attractive.[2a] An elegant synthesis of these macrolides has been reported by Smith and co-workers in which the C1–C11 fragment was prepared in 19 steps from L-malic acid.[2]

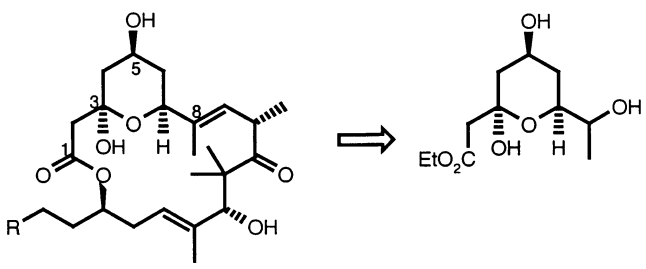
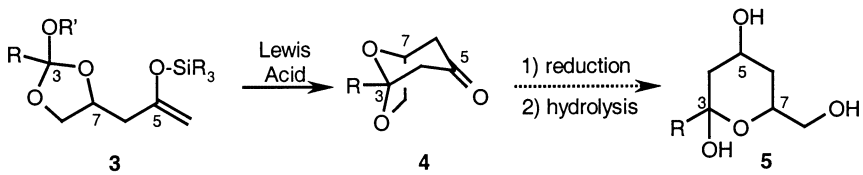


Figure 1.

We have been interested in an intramolecular reaction between silyl enol ethers and *ortho* esters,[3] which give rise to rigid bicyclic acetals like structure **4** (Scheme 1).[4] This concept can be applied to the preparation of pyran ring systems bearing structural features found in the C1–C8 segment of acutiphycin. Similar approaches have been used successfully for the synthesis of other natural products.[5]

Since a variety of silyl enol ethers–*ortho* esters can be easily prepared, this reaction becomes a versatile tool to give access to highly functionalized ring systems. Modification of the substituent R on the *ortho* ester of **3** will determine the substitution obtained at the anomeric position of **5**. Consequently the C1–C3 segment of acutiphycin can be introduced by the preparation of the appropriate *ortho* ester (**3**, $R = CH_2–CO_2R$). In addition, the rigidity of the bicyclic intermediate **4** allows for complete stereocontrol of the C-5 alcohol resulting from the reduction of the ketone. Finally, the stereochemistry at C-7 will determine the relative stereochemistry that can be obtained at C-3 and C-5.



Scheme 1.

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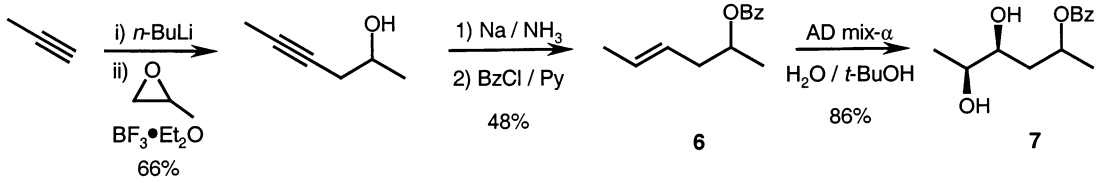


Scheme 2.

The first requirement is the preparation of the appropriate carbon skeleton which was achieved in four steps starting with propyne (Scheme 2). The stereochemistry of the benzoyl-protected alcohol in **7** is not important since it will be used at a later stage to generate the required silyl enol ether. This benzoate protecting group gave superior chemical stability over an acetate under the reaction conditions of the Sharpless dihydroxylation.

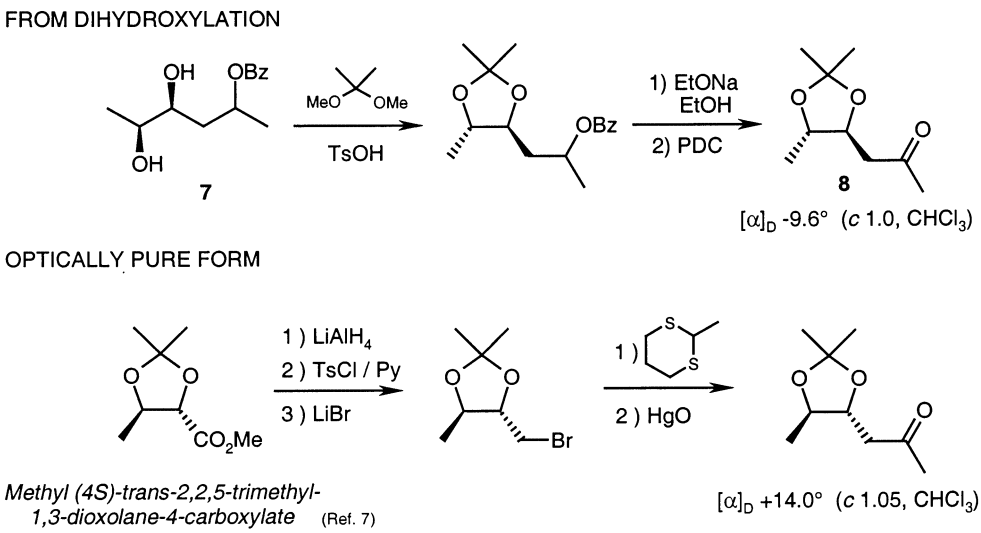
The absolute stereochemistry of the target product is dependent on the induction observed during the Sharpless dihydroxylation. Thus, it is important to confirm the level and the direction of the induction obtained. These two parameters were determined by converting **7** to a compound (**8**) that contains only the chirality generated during the dihydroxylation. Then a comparator molecule was prepared in an optically pure form (Scheme 3).[6] Optical rotation measurements confirmed the expected absolute configuration and established the enantiomeric excess to be 69%.

The degree of asymmetric induction observed for the dihydroxylation of **6** is considerably lower than that of comparable examples reported in the literature.[8] This may be due to interference from the benzoyl group with the cinchona-based ligand of the AD-mix reagent in its approach to the olefin. Other ligands have not been explored.[9]

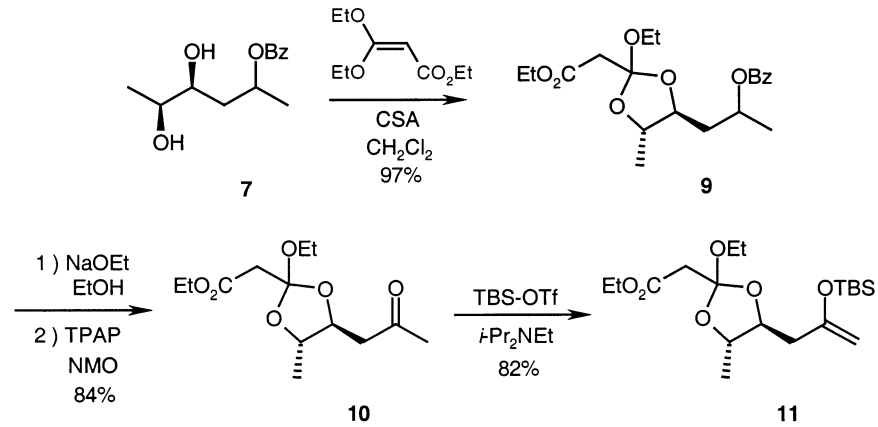
The C1–C3 segment was introduced on the diol **7** by a Michael addition onto ethyl 3,3-diethoxyacrylate followed by a *trans ortho*-esterification to give the cyclic *ortho* ester **9** (Scheme 4). The benzoyl protected alcohol of **9** is then ready for conversion to the silyl enol ether via **10**. Using TBSOTf and Hunig's base, the silyl enol ether (disubstituted olefin) **11** resulting from kinetically controlled deprotonation was obtained. None of the thermodynamic product (trisubstituted olefin) was observed by NMR.

For the key cyclization of **11**, several commonly used Lewis Acids were studied. Both the quantity of Lewis acid and the temperature were evaluated to reach the best compromise between silyl enol ether activation and dioxonium formation. Mild acids like $Zn(OTf)_2$ led to rearrangement of the silyl enol ether **11** to an α,β-unsaturated ketone while strong acids like $AlCl_3$ gave only decomposition products. Representative reaction conditions are summarized in Table 1.

The target C1–C8 fragment was accessed in two steps from the bicycloketone **12** (Scheme 5). First the stereoselective reduction of the ketone provided the axial alcohol **13**. Subsequent acid hydrolysis of the bicyclic ketal gave the target hemiketal **14**.[10] Under these hydrolysis conditions, the C1–C3 side chain equilibrates to the equatorial position giving the stereochemistry encountered in acutiphycin for this chiral center.

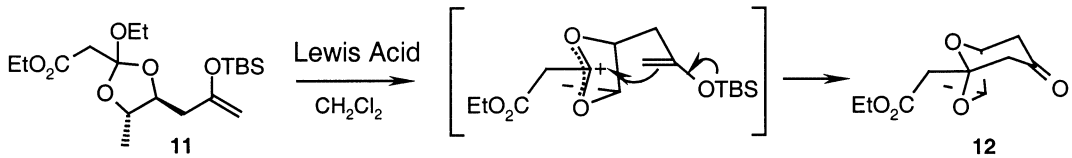


Scheme 3.

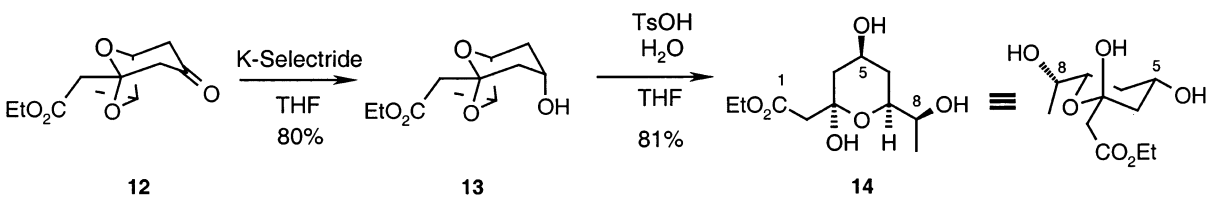


Scheme 4.

Table 1. Reaction conditions of the intramolecular cyclization



Lewis acid	Equiv. of Lewis acid	Temperature (°C)	Isolated yield (%)
$EtAlCl_2$	1.5	−78 to −15	20
Et_2AlCl	1.5 or 3.2	−78 to −15	50
$BF_3{\cdot}Et_2O$	1.5	−78 to −15	58
$Ti(O\text{-}i\text{-}Pr)_3Cl$	1.5	−78 to −15	0
$TiCl_4$	1.5	−48	38
$TiCl_4$	1.5	−78	65
$TiCl_4$	1.5	−91	49



Scheme 5.

In conclusion, the synthesis of the C1–C8 segment of (+)-acutiphycin was achieved in 11 steps with an overall yield of 17%. This synthesis illustrates the efficiency and the versatility of the intramolecular silyl enol ether–*ortho* ester reaction to generate a bicyclic system with the appropriate functionality and good stereocontrol.

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10. Spectral data for novel representative compounds: Compound **12**: ^{1}H NMR (CD_3COCD_3, 500 MHz) δ 1.13 (d, 3H, $J=6.2$ Hz), 1.22 (t, 3H, $J=7.1$ Hz), 2.40 (dt, 1H, $J=16.6$, 1.2 Hz), 2.62 (dt, 1H, $J=16.2$, 0.8 Hz), 2.69 (dd, 1H, $J=16.6$, 5.2 Hz), 2.82 (m+s, 1H+2H), 4.08 (q, 1H, $J=6.2$ Hz,), 4.11 (q, 2H, $J=7.1$ Hz), 4.49 (d, 1H, $J=5.2$); ^{13}C NMR (CD_3COCD_3, 125 MHz) δ 14.3, 21.3, 44.0, 46.1, 51.7, 60.8, 78.5, 78.8, 107.4, 168.7, 204.4; HRFABMS m/z 229.1075, calcd for $C_{11}H_{16}O_5$ $(M+H)^+$ 229.1076. Compound **14**: ^{1}H NMR (CD_3COCD_3, 500 MHz) δ 1.06 (d, 3H, $J=6.4$ Hz), 1.18 (m, 1H), 1.22 (t, 3H, $J=7.1$ Hz), 1.36 (m, 1H), 1.86 (m, 1H), 2.09 (m, 1H), 2.62 (AB, 1H, $J=14.4$ Hz), 2.65 (AB, 1H, $J=14.4$ Hz), 3.13 (d, 1H), 3.56 (m, 1H), 3.69 (m, 1H), 3.77 (d, 1H), 4.05 (m, 1H), 4.12 (q, 2H, $J=7.1$ Hz), 4.97 (d, 1H); ^{13}C NMR (CD_3COCD_3, 100 MHz) δ 14.3, 18.7, 36.7, 44.1, 46.5, 60.8, 64.1, 69.8, 73.8, 97.1, 171.4; HRFABMS m/z 287.0896, calcd for $C_{11}H_{20}O_6$ $(M+K)^+$ 287.0897. Relative stereochemistry of **14** was determined by COSY and NOE experiments.