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A Highly Diastereoselective Aldol Reaction of Dicobalt Hexacarbonyl Propynal Complex and Uncomplexed Propynal: A Stereoselective Divergent Synthesis of (±)-PS-5 and (±)-6-Epi-PS-5

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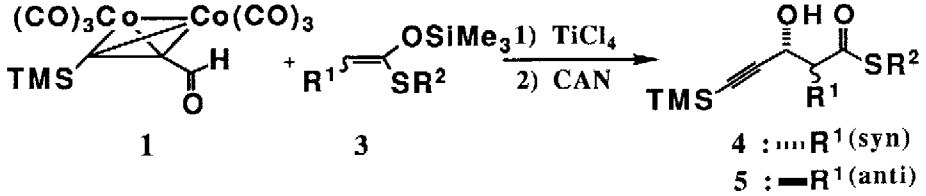
Key Words: Nicholas reaction; cobalt complexed propynal; uncomplexed propynal; (±)-PS-5; (±)-6-epi-PS-5

Abstract: *The aldol reaction of cobalt complexed propynal 1 with O-silyl ketene O,S-acetals 3 gave the syn-products exclusively, while the uncomplexed propynal 2, the corresponding anti-compounds. A successful application of these stereoselective reactions to a synthesis of (±)-PS-5 and (±)-6-epi-PS-5 is described.*

Propargyl cations stabilized with binuclear cobalt species are subject to nucleophilic attack at the propargyl position (Nicholas reaction).[1] This reaction has been utilized for a construction of complex molecules.[2] Recently taking advantage of this useful property of the cobalt complex, we[3] and another group[4] have independently introduced the propynal-cobalt complexes into the aldol reaction[5] with *O*-silyl enol ethers. In order to develop more efficient and selective reactions mediated by cobalt complexation, we investigated the aldol reaction between the cobalt complexed propynal and *O*-silyl ketene *O,S*-acetals. Disclosed herein are (i) a highly *syn*-selective aldol reaction of the cobalt complexed propynal, (ii) a highly *anti*-selective aldol reaction of the uncomplexed propynal,[6] and (iii) an application of these reactions to a divergent synthesis of β-lactam antibiotics, (±)-PS-5 and (±)-6-epi-PS-5.



1 3

4 : R1 (syn)
5 : R1 (anti)

a: R^1=Me, R^2=Bu^t; **b:** R^1=Me, R^2=Ph; **c:** R^1=Et, R^2=Bu^t; **d:** R^1=Pr^i, R^2=Bu^t

Table 1. Aldol Reaction of the Cobalt Complexed Propynal 1 with *O*-Silyl Ketene *O,S*-Acetal 3 in the Presence of $TiCl_4$

entry	*O*-silyl ketene *O,S*-acetal 3	R^1	R^2	*E* : *Z*[a]	yield (%)	4 5 *syn* : *anti*[a,b]
1	**a**	Me	Bu^t	>98 : <2	90	>98 : <2
2	**a**	Me	Bu^t	5 : 95	84	>98 : <2
3	**b**	Me	Ph	<2 : >98	89	>98 : <2
4	**c**	Et	Bu^t	92 : 8	89[c]	>98 : <2
5	**c**	Et	Bu^t	8 : 92	93	>98 : <2
6	**d**	Pr^i	Bu^t	<2 : >98	—[d]	

[a] Determined by 400 or 500 MHz ^{1}H-NMR spectra. [b] No *anti*-isomer could be detected in ^{1}H-NMR spectra. [c] $BF_3{\cdot}OEt_2$ was used instead of $TiCl_4$. [d] No reaction took place.

The cobalt complexed propynal **1**[3] easily prepared from the reaction of **2** with dicobalt octacarbonyl was allowed to react at -78°C with *O*-silyl ketene *O,S*-acetals **3** in dry methylene chloride in the presence of titanium (IV) chloride to afford the aldol products with the cobalt moiety, which were subsequently decomplexed with cerium(IV) ammonium nitrate (CAN)[7] in methanol at 0°C resulting in the exclusive formation of *syn*-isomers **4**.[8] The results are summarized in Table 1. The *syn*-products **4** were exclusively obtained in high yields in all cases (except for entry 6). The degree of *syn*-selectivity did not depend on the geometry of the starting **3**. When **3d** (R^1=Pr^i, R^2=Bu^t) was submitted to the aldol reaction, no reaction took place at all and **3d** was completely recovered.

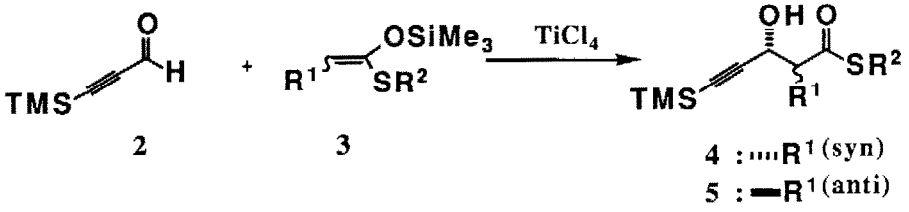


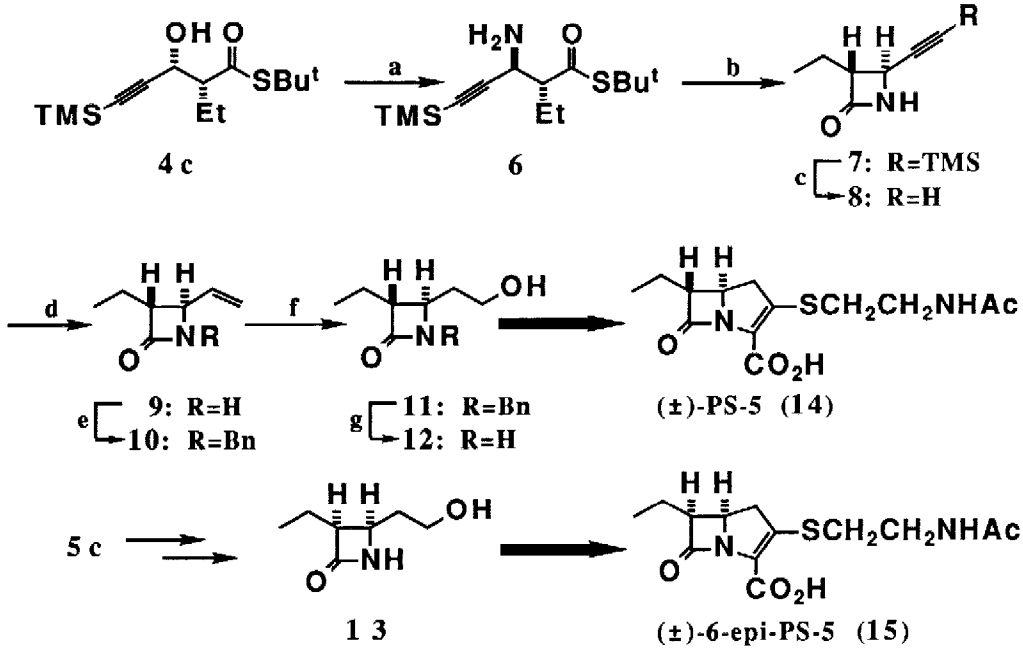
Table 2. Aldol Reaction of an Uncomplexed Propynal 2 with O-Silyl Ketene *O,S*-Acetal 3 in the Presence of $TiCl_4$

entry	*O*-silyl ketene *O,S*-acetal 3	R^1	R^2	*E* : *Z*[a]	yield (%)	4 5 *syn* : *anti*[a]
1	**a**	Me	Bu^t	>98 : <2	87	5 : 95
2	**a**	Me	Bu^t	5 : 95	86	4 : 96
3	**b**	Me	Ph	<2 : >98	87	<2 : >98[b]
4	**c**	Et	Bu^t	92 : 8	74	<2 : >98[b]
5	**c**	Et	Bu^t	8 : 92	92	<2 : >98[b]
6	**d**	Pr^i	Bu^t	<2 : >98	70	27 : 73

[a] Determined by 400 or 500 MHz ^{1}H-NMR spectra. [b] No *syn*-isomer could be detected in ^{1}H-NMR spectra.

On the other hand, the aldol reaction of an uncomplexed propynal **2** with **3** under similar conditions described for **1** except for treatment with CAN yielded the *anti*-isomers **5**[8] in a highly stereoselective manner regardless of the geometry of **3** (Table 2). These results are in marked contrast to ones obtained from the reaction of **2**[3] with *O*-silyl enol ethers where the reaction proceeded nonselectively. It should be mentioned that the *anti*-selectivity diminished greatly in the case of **3d** (R^1=Pr^i, R^2=Bu^t).

The above highly stereoselective reactions were then successfully applied to a synthesis of (±)-PS-5 and (±)-6-epi-PS-5. The Mitsunobu reaction[9] of the *syn*-aldol product **4c** furnished the *anti*-azide compound, which was in turn reduced with triphenylphosphine and water[10] to give **6** in 68% yield. The azetidinone ring formation was realized by successive treatment of **6** with trimethylsilyl chloride and *tert*-butylmagnesium chloride to give the azetidinone **7**[11] in 82% yield. Desilylation of **7** with fluoride anion (86%), followed by partial hydrogenation in the presence of Lindlar catalyst afforded the vinyl derivative **9** (90%). On treatment with benzyl bromide, **9** provided the N-protected product **10** (80%), hydroboration and oxidation of which gave **11** in 75% yield. Finally debenzylation of **11** with sodium in liquid ammonia produced the desired hydroxy-amido derivative **12**[12] in 82% yield. Similar sequential procedures[13] were applied to the *anti*-aldol product **5c** yielding the 3-epi-analogue **13**.[14] Since (+)-**12**[12] and (±)-**13**[14] have already been converted into (+)-PS-5 and



(a) (i) HN_3, PPh_3, DEAD, C_6H_6, r.t.; (ii) PPh_3, H_2O, THF, 60°, 15h, 68%; (b) Et_3N, TMSCl, 0°→r.t., then ^{t}BuMgCl, 0°→r.t., 18h, 82%; (c) TBAF, THF, -78°→r.t., 86%; (d) H_2, Lindlar catalyst, MeOH-hexane (1:20), r.t., 30 min, 90%; (e) NaH, THF, 0°, 15 min, then BnBr, r.t., 1h, 80%; (f) (i) Sia_2BH, THF, 0°, 2h; (ii) H_2O_2, NaOH, 0°→r.t., 1h, 75%; (g) Na, liq. NH_3, THF, -78°, 1h, 82%.

(±)-6-epi-PS-5, respectively, the present synthesis of both (±)-**12** and (±)-**13** amounts to a synthesis of (±)-PS-5 and (±)-6-epi-PS-5.

In summary, we developed a highly *syn*-selective aldol reaction between the cobalt complexed propynal and *O*-silyl ketene *O,S*-acetals irrespective of the geometry of the latter. The uncomplexed one in the aldol reaction was found to bring about a reverse selectivity resulting in the exclusive formation of the *anti*-isomers. Furthermore we demonstrated the potentiality of these reactions by synthesis of β-lactam antibiotics, (±)-PS-5 and (±)-6-epi-PS-5.

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