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# An Optically Active Chromium(0)-Complexed Benzaldehyde in Organic Synthesis: A Highly Stereocontrolled Asymmetric Synthesis of (2R,3S)-(-)-*N*-Benzoyl-3-phenylisoserine Methyl Ester, the Taxol C-13 Side Chain Analogue

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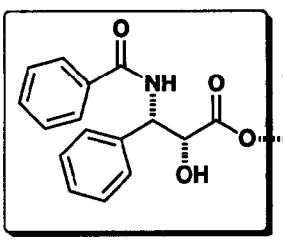
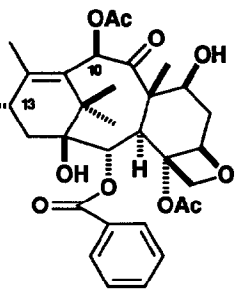
**Abstract:** An asymmetric aldol reaction of (+)-chromium(0)-complexed benzaldehyde **4** with the titanium enolate generated from the ethanethioate **5** provided the *anti*-aldol product **6** in a highly stereoselective manner, which was subsequently converted to the taxol C-13 side chain.

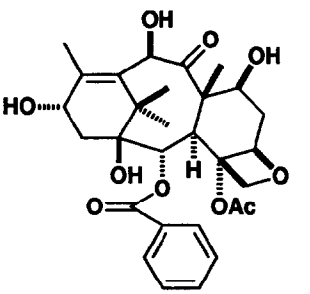
Taxol (**1**), isolated from the bark of *Taxus brevifolia*,[1] is the most promising anti-tumor agent[2-4] that has exhibited impressive efficacy in clinical trials. An extremely potent anti-tumor property of taxol (**1**) combined with its strikingly complex and strained structure has now made itself one of the most exciting and challenging compounds. Although taxol (**1**) can be obtainable in only low yield from natural resources, its precursor in a semisynthetic supply, 10-deacetylbaccatin III (**2**)[5] has been recently shown to be more readily available.




(2R,3S)-*N*-benzoyl-3-phenylisoserine moiety

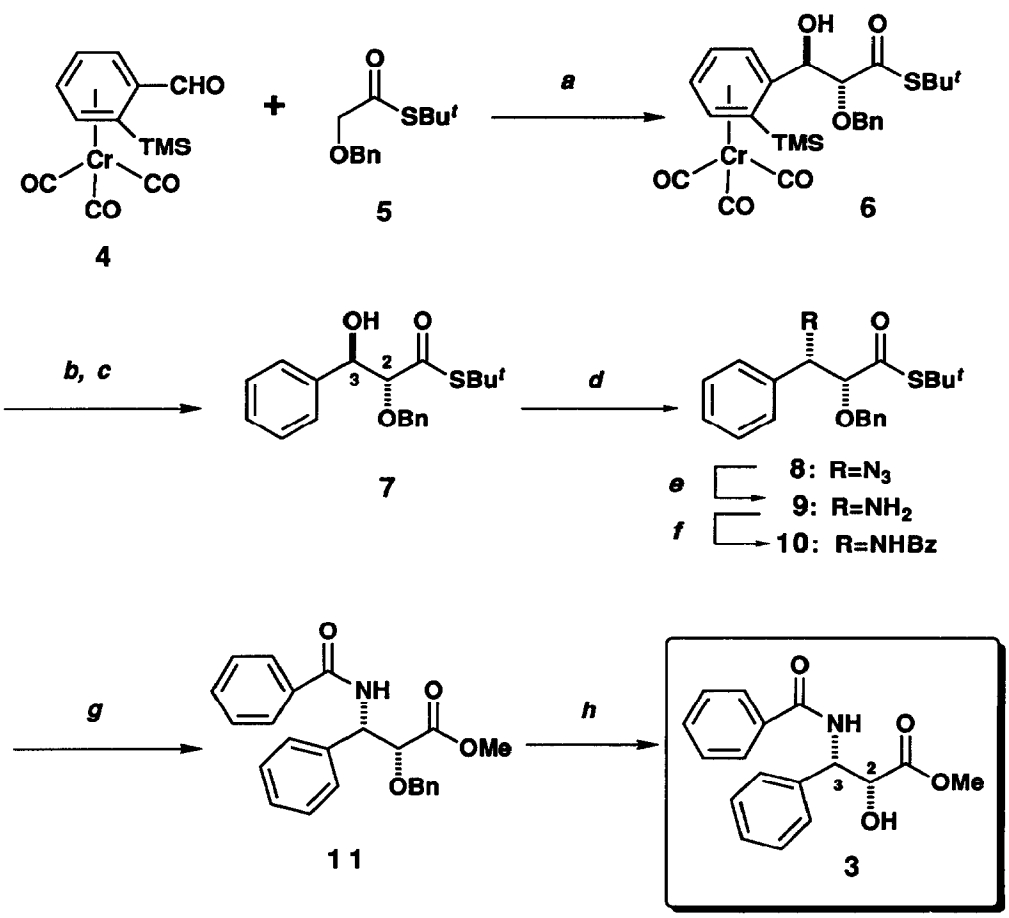



**Taxol (1)**




**10-Deacetylbaccatin III (2)**

Concerning to enough supply of taxol (**1**) at the clininal stage, the relatively easy availability of 10-deacetylbaccatin III (**2**) has stimulated us to develope an efficient and enantioselective synthesis of the taxol C-13 side chain, (2R,3S)-*N*-benzoyl-3-phenylisoserine residue which has been elucidated to be crucial for the strong anti-tumor activity of taxol (**1**). Two groups[6,7] have so far reported the enantioselective synthesis of the taxol C-13 side chain. We describe herein an alternative and highly stereocontrolled synthesis of (2R,3S)-(-)-*N*-benzoyl-3-phenylisoserine methyl ester (**3**)[6b,c] through a highly stereoselective asymmetric aldol reaction of the chromium(0)-complexed *o*-TMS-benzaldehyde **4** as a key step.




(*a*) $TiCl_4/Et_3N/CH_2Cl_2$, -78°C; (*b*)TBAF-HF/$CH_3CN$-THF, -78°C to 0°C; (*c*) hυ/$Et_2O$, 0°C; (*d*) $HN_3/PPh_3$/DEAD/$C_6H_6$, r.t.,THF; (*e*)$PPh_3/H_2O$/THF, 60°C; (*f*) BzCl/DMAP/$CH_2Cl_2$, 0°C; (*g*) $Tl(ONO_2)_3.3H_2O$/MeOH, 25°C; (*h*)10%Pd-C/$H_2$/EtOH, 60°C.

(+)-Tricarbonyl($\eta^6$-*o*-trimethylsilylbenzaldehyde)chromium(0) complex (**4**)[8,9] was treated with the titanium enolate[10] generated *in situ* by the reaction of the ethanethioate **5**[11] with titanium tetrachloride and triethylamine in dry methylene chloride at -78°C to afford the *anti*-aldol condensation product **6**[12,13] with chromium complexation in 93% yield. Desilylation of the aldol product **6** with tetrabutylammonium fluoride and hydrofluoric acid in tetrahydrofuran and acetonitrile, followed by decomplexation by short irradiation with ≥300 nm light in diethyl ether produced **7**[12] in 63% yield.

The next phase of our strategy for the synthesis of phenylisoserine derivative required introduction of the amino functionality with stereo inversion at the C-3 position of **7**. The Mitsunobu reaction[14] of **7** with hydrazoic acid, diethyl azodicarboxylate, and triphenylphosphine gave the *syn*-azide compound **8**,[15] which was subsequently reduced with triphenylphosphine and water to furnish the corresponding amino derivative **9**.[15] The benzoylation of **9** with benzoyl chloride and 4-*N*,*N*-dimethylaminopyridine yielded **10** [mp 138 - 139°C; $[\alpha]^{23}_D$ +58.5 (*c*, 0.41, $CHCl_3$), >98% e.e.[16,17]] as a both diastereomerically and enantiomerically pure form in 63 % yield. Thioester functionality of **10** could be easily converted into the corresponding methyl ester **11** [mp 103-105°C; $[\alpha]^{22}_D$ -5.3 (*c*, 0.41, $CHCl_3$); >98% e.e[16,17]] in a quantitative yield by exposure of **10** to thallium trinitrate[18] in methanol.

Finally, the benzyl group on the C-2 hydroxy group of compound **11** was reductively removed with 10% palladium-carbon under hydrogen atmosphere to provide (2R,3S)-(-)-*N*-benzoyl-3-phenylisoserine methyl ester (**3**)[mp 180 - 182°C; $[\alpha]^{20}_D$ -48.1 (*c*, 0.28, MeOH), >98% e.e.[17,19] lit.[6b] mp 183-185°C; $[\alpha]^{26}_D$ -48 (*c*, 0.92, MeOH)] in 78% yield.

Thus, we have completed a highly stereocontrolled synthesis of (2R,3S)-(-)-*N*-benzoyl-3-phenylisoserine methyl ester (**3**), a crucial moiety of taxol (**1**) for strong anti-tumor activity, from (+)-chromium(0)-complexed benzaldehyde derivative **4**. This synthesis provides an alternative and efficient way for the preparation of the taxol (**1**) C-13 side chain, (2R,3S)-*N*-benzoyl-3-phenylisoserine moiety.

## REFERENCES AND NOTES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11. The titanium enolate of methyl benzyloxyacetate also effected the aldol reaction with **4**, but the observed diastereoselectivity was much lower than the case of the ethanethioate **5**.
12. A mixture of the *anti*- and *syn*-isomer in a ratio of 95 to 5 (from $^1$H NMR spectra) was obtained. This mixture was carried to the next stage without isolation.
13. Interestingly the aldol reaction of (±)-**4** with the lithium enolate of the ethanethioate **5** proceeded *syn*-selectively to furnish, after decomplexation, a mixture of the racemic *anti-o*-TMS derivative of **7** and the corresponding *syn*-product in a ratio of 20 to 80. On the other hand, *O*-trimethylsilyl ketene *O,S*-acetal of **5** under the Mukaiyama condition didn't give any aldol products. These results will be presented in detail somewhere else.
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15. A mixture of the *syn*- and *anti*-isomer in a ratio of 95 to 5 (from $^1$H NMR spectra) was obtained.
16. The enantiomeric excess was determined by $^1$H NMR spectra using a shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III).
17. No peak of the antipode could be detected by $^1$H NMR spectra.
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