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Advances in the vinylogous Mukaiyama aldol reaction and its application to the synthesis of the C1–C7 subunit of oleandolide

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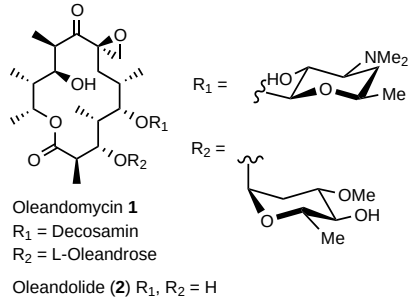
Abstract—The synthesis of a stereo pentade of the macrolide antibiotic oleandolide is reported. The C1–C7 fragment resembles the analogous segment of Panek's total synthesis of oleandolide. The use of the vinylogous Mukaiyama aldol reaction shortens the route significantly and has the advantage of utilizing an easily accessible ketene acetal.

Polyketides are a class of natural products which represent a great variety of compounds with promising biological activities. Oleandomycin (**1**), a 14-membered macrolide antibiotic, was isolated from the actinomycete *Streptomyces antibioticus* by Sobin et al.[1] in 1955. In 1960 the structure was reported by Celmer, Woodward and co-workers.[2] Its absolute configuration was determined in 1965[3] and independently confirmed by X-ray analysis.[4] Oleandomycin unravels its biological activity by binding to the 50-S ribosomal subunit and interfering with the transpeptidation or translocation reaction[5] (Scheme 1).

Four total syntheses have been reported. Tatsuta[6] et al. reconstructed oleandomycin from its aglycon which they derived by degradation from the natural product. Paterson[7] and Evans[8] reported total syntheses of oleandolide through their aldol chemistry and Panek used his chiral crotylsilane approach for a highly convergent total synthesis. Even though the methods utilized are widely employed in other natural product syntheses and characterized by their general applicability and reliability, one would appreciate steps in which larger building blocks can be assembled to pivotal fragments (Scheme 2).[9]



Scheme 1. Structures of oleandomycin (**1**) and its aglycon oleandolide (**2**).

We could demonstrate that the vinylogous Mukaiyama aldol reaction with ketene acetal **6** can be applied to give good Felkin-control and *syn*-selectivity in the case of aldehyde **15**.[10] The poor *syn*-selectivity (*syn*:*anti*= 1:1) observed in the addition of **9** to **7** seems to reflect the double bond geometry of the ketene acetal. In previous experiments with ketene acetal **6** we found that the 3,4-*Z* configuration is essential not only for obtaining good yields but also for the *syn*-selective addition (Scheme 3).

On the other hand, the addition of **6** to **7** gives exclusively the all-*syn* diastereomer (**8**). The use of tris(pentafluorophenyl)borane (TPPB) in the presence of isoproyl alcohol as a SiR_3^+-scavenger is essential for the *syn*-selectivity in contrast to additions without isoproyl alcohol in which TBS^+ acts as the catalyst. As a probe for this hypothesis we tried to catalyze the aldol reaction with TBSOTf. As expected, only moderate *syn*-selectivity (4.5:1) was observed, also witnessed under isopropyl alcohol free conditions in the reaction of **6** and **7** (Scheme 4).

In order to demonstrate the efficiency of the vinylogous Mukaiyama aldol reaction we report the synthesis of the C1–C7 segment of oleandolide which could be used

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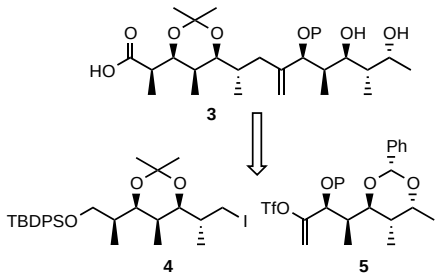
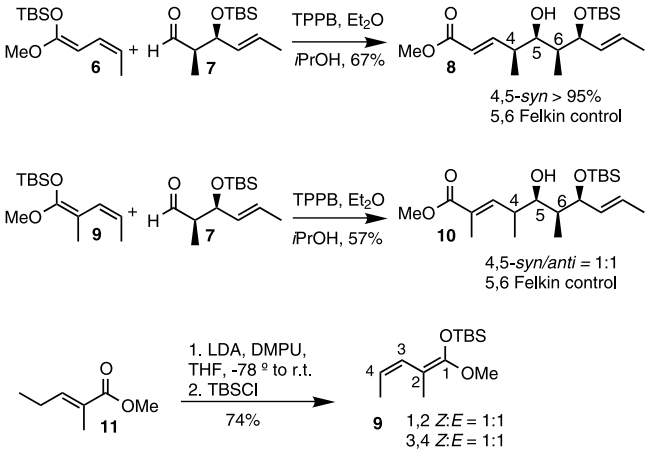
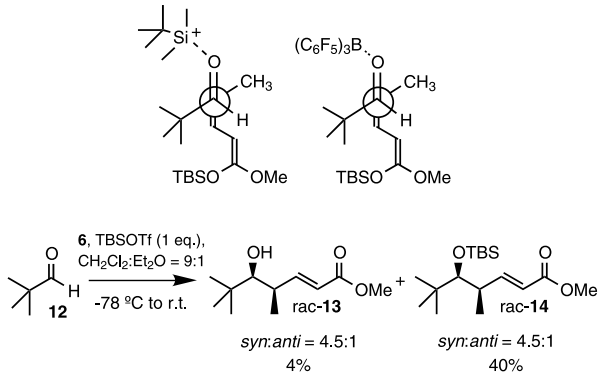


Scheme 2. Retrosynthetic analysis of Panek's oleandolide synthesis.

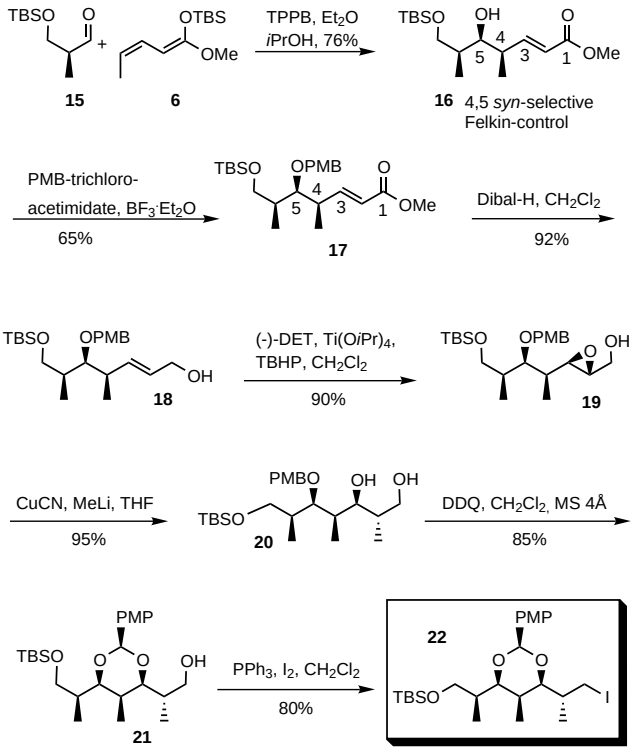


Scheme 3. Application of the vinylogous Mukaiyama aldol reaction to α-chiral aldehydes with different ketene acetals.



Scheme 4. TBSOTf-catalyzed vinylogous Mukaiyama aldol reaction.

in Panek's total synthesis of oleandolide. The key step is the *syn*-selective Felkin-controlled addition of ketene acetal **6** to the Roche aldehyde **15** (Scheme 5).[11] The selective addition requires tris(pentafluorophenyl)-borane as the Lewis acid and isopropyl alcohol as a scavenger for the Si^{+}-species. The resulting secondary alcohol (**16**) was PMB-protected with PMB–trichloroacetimidate and $BF_3{\cdot}Et_2O$. Ester reduction with Dibal-H and subsequent Sharpless epoxidation using (–)-DET furnished compound **19** in 90% yield. Epoxide opening was achieved with CuCN/MeLi to provide the stereo pentade **20** in 95% yield. Treatment



Scheme 5. Synthesis of the C1–C7-fragment of oleandolide.

with DDQ in the absence of water provided benzylidene acetal **21** which was transformed into the corresponding iodide (**22**) with I_2 and PPh_3.[12]

This sequence of just seven steps starting from aldehyde **7** can be performed on large scale and constructs four asymmetric carbons with an overall yield of 26.4%.

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11. Aldehyde **15** (44 mg, 0.217 mmol) dissolved in ethyl ether (2 mL) was cooled to −78°C under argon. Tris(pentafluorophenyl)borane (111 mg, 0.217 mmol) was added and a mixture of ketene acetal **6** (100 mg, 0.438 mmol) and isopropyl alcohol (17 μL, 0.24 mmol) dissolved in ethyl ether (1 mL) was added over 6 h. After completion, the cold reaction mixture was directly poured on a silica gel column. Flash chromatography using ethyl acetate/hexanes (1:4) as eluant afforded 52 mg (0.164 mmol, 76%) of **16** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, $J=15.7$, 9.3 Hz, 1H), 5.83 (dd, $J=15.7$, 0.9 Hz, 1H), 3.76 (dd, $J=9.8$, 3.1 Hz, 1H), 3.69 (s, 3H), 3.64 (dd-like, $J=8.7$, 1.3 Hz, 1H), 3.62 (dd, $J=9.8$, 3.9 Hz, 1H), 3.38 (broad s, 1H), 2.43 (dtq-like, $J=9.3$, 6.6, 0.9 Hz, 1H), 1.57–1.66 (m, 1H), 1.12 (d, $J=6.6$ Hz, 3H), 0.91 (d, $J=7.0$ Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 151.1, 120.8, 77.8, 69.2, 51.4, 40.9, 26.6, 25.8, 18.1, 16.7, 9.3, −5.6, −5.7.
12. To a stirred solution of triphenylphosphine (12 mg, 0.046 mmol) and imidazole (4 mg, 0.055 mmol) in DCM (0.5 mL) at 0°C, iodine (17 mg, 0.07 mmol) was added. After 5 min, alcohol **21** (5 mg, 0.01 mmol) was added in CH_2Cl_2 (0.3 mL) and the mixture was stirred at room temperature for 17 h. Saturated aqueous $Na_2S_2O_3$ (1 mL) was added, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with 1 M aqueous $NaHSO_4$ (1 mL), dried with $MgSO_4$, filtered through Celite and evaporated in vacuo. Flash column chromatography with petrol ether as eluant afforded iodide **22** (5 mg, 0.009 mmol, 80%) as a white solid. $[\alpha]_{20}^{D}$ −9.25 ($c=0.4$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, $J=8.7$ Hz, 2H), 6.87 (d, 8.7 Hz, 2H), 5.46 (s, 1H), 3.78 (s, 3H), 3.59 (dd, $J=9.7$, 2.0 Hz, 1H), 3.57 (dd, $J=10.0$, 4.5 Hz, 1H), 3.51 (dd, $J=9.4$ Hz, 1H), 3.50 (dd, $J=10.0$, 4.3 Hz, 1H), 3.46 (dd, $J=9.8$, 2.0 Hz, 1H), 3.40 (dd, $J=9.4$, 2.8 Hz, 1H), 1.94–1.86 (m, 1H), 1.78 (dq-like, $J=6.8$, 2.0 Hz, 1H), 1.51–1.46 (m, 1H), 1.05 (d, $J=6.7$ Hz, 3H), 0.97 (d, $J=6.8$ Hz, 3H), 0.90 (d, $J=6.7$ Hz, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 131.7, 127.2, 113.5, 101.5, 84.0, 83.9, 64.5, 55.3, 36.6, 34.7, 30.9, 26.9, 25.9, 18.2, 15.8, 14.4, 7.0, −5.5, −5.6; HRMS calcd for $C_{24}H_{41}IO_4Si$: 548.1819, found: 548.1807.