Thieme Chemistry Journal Awardees– Where are They Now? An Asymmetric Organocatalytic Sequence towards 4a-Methyl Tetrahydroxanthones: Formal Synthesis of 4-Dehydroxydiversonol

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Abstract: Tricyclic systems generated by an asymmetric vinylogous aldol–oxa-Michael reaction of salicylaldehydes with senecialdehyde were further elaborated using a strategy developed by Tietze et al. to generate 4a-methyl tetrahydroxanthones.

Key words: domino vinylogous aldol–oxa-Michael reaction, Wittig reaction, natural products

Organocatalytic domino reactions have recently attracted much attention due to the mild and straightforward access to complex structures that they provide.[1] The domino reaction of salicylaldehydes **1** with α,β-unsaturated aldehydes **2** has been recently investigated in light of their use in total synthesis of natural products.

Depending on the reaction conditions, in most cases an oxa-Michael–aldol reaction occurs to give chromenes **3**. However, under a yet different set of conditions, we and others have discovered that rigid tricyclic systems **4** are formed by a vinylogous aldol–oxa-Michael reaction (Scheme 1).[2]

Recently, the Woggon group elaborated an organocatalytic procedure which at the end culminated in an elegant total synthesis of α-tocopherol (**6**).[3]

In the meantime, the Tietze group developed a yet different approach for the synthesis of chromanes which was based on an asymmetric Wacker–Heck reaction. They were able to convert these building blocks into tocopherols[4] and, very recently, into tetrahydroxanthones like 4-dehydroxydiversonol (**5**).[5–7]

In this paper we explore the chemistry of the tricycles **4** to show the compatibility of both approaches.

The required salicylaldehydes are mostly commercially available. Salicylic aldehyde **1b** can be derived from orcinol over three steps in an overall yield of 70% according to a literature procedure.[6a]

The reaction of salicylaldehydes **1** with senecialdehyde (**2a**) gave the tricycles **4** in good to very good yields. The wide scope of this type of reaction is shown in Table 1.

It is interesting to note that under yet similar conditions, salicylaldehyde **1b** gave the best yield. The structure of **4b** was confirmed by X-ray crystallography (CCDC-717754, Figure 1)[8].

Using Jørgensen's proline-derived organocatalyst[3,9] – (*S*)-bis-[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanoltrimethylsilyl ether – we were able to obtain the tricycle **4a** in 66% yield with an ee value of 98%.

Stefan Bräse was born in Kiel, Germany in 1967. After he studied in Göttingen, Bangor (UK) and Marseille, he received his Ph.D. in 1995, after working with Armin de Meijere in Göttingen. After post-doctoral appointments at Uppsala University (Jan E. Bäckvall) and The Scripps Research Institute, La Jolla (K. C. Nicolaou), he began his independent research career at the RWTH Aachen (Germany) in 1997 (associated to Dieter Enders). In 2001, he finished his Habilitation and moved to the University of Bonn as Professor for Organic Chemistry. Since 2003, he is full professor at the University of Karlsruhe, Germany. He is recipient (among other awards) of the OrChem award of the GDCh and the Lilly award. His research interests include methods in drug-discovery (including drug-delivery), combinatorial chemistry towards the synthesis of biologically active compounds, total synthesis of natural products and nanotechnology.

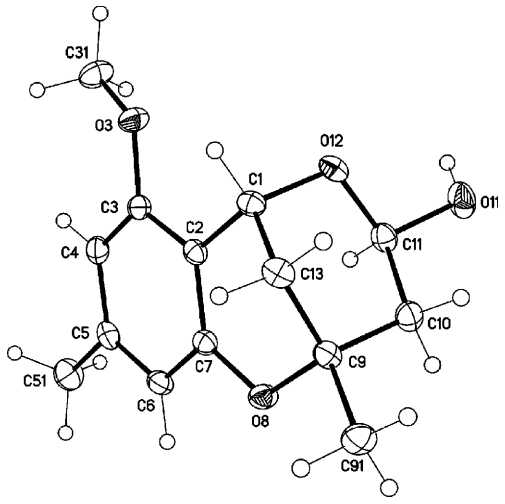

Figure 1 Molecular Structure of **4b**. Displacement parameters are drawn at 50% probability level

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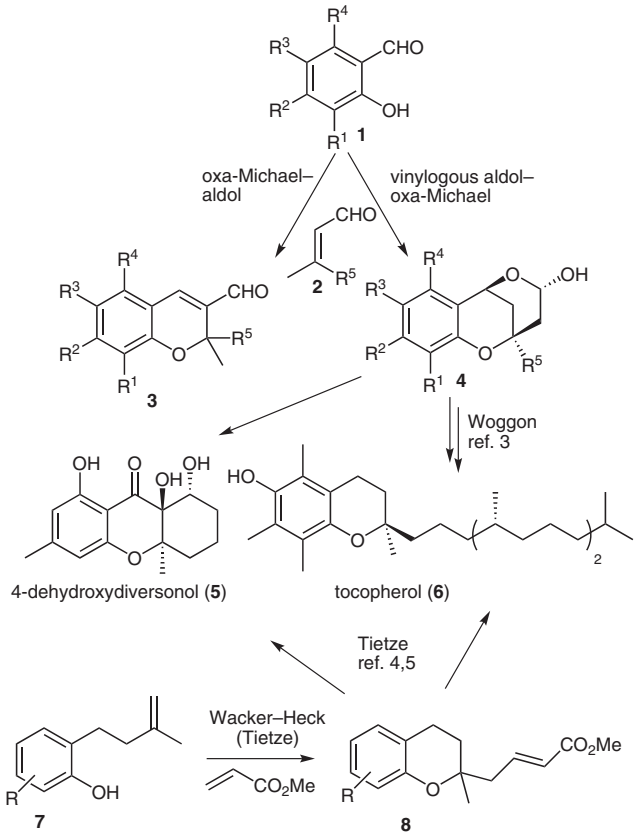
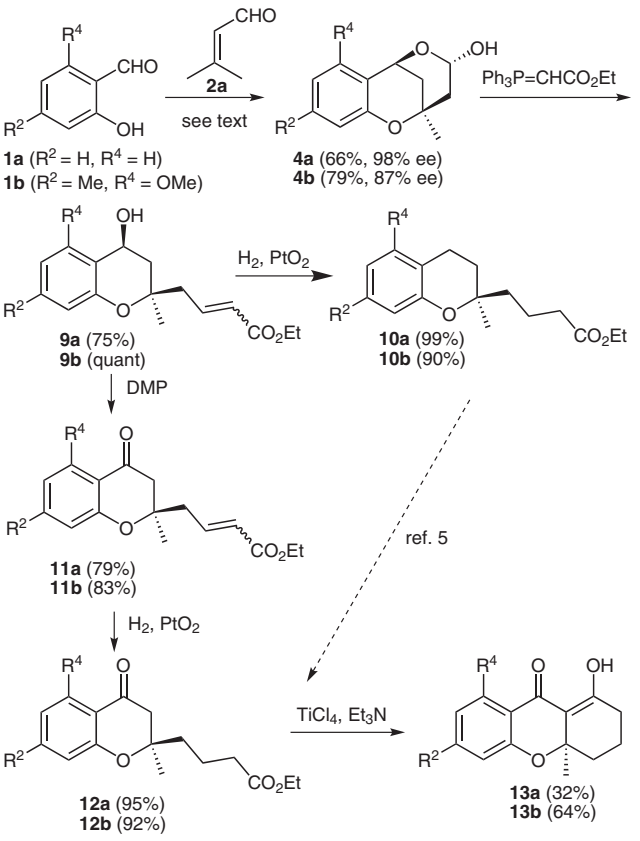


Scheme 1 Strategies for the synthesis of chromenes based on α,β-unsaturated aldehydes **2**



Scheme 2 Conversion of salicylaldehydes **1** into xanthones **13**[10]

Table 1 Scope of the Oxa-Michael–Aldol and Vinylogous Aldol-oxa-Michael Reaction of Salicylaldehydes **1** with Senecialdehyde (**2a**, R^5 = Me)[a]

Entry[b]	Salicylaldehyde (**1**)					Cond.[a]	Yield (%)	
	1	R^1	R^2	R^3	R^4		**3**	**4**
1	**1a**	H	H	H	H	A	19	46
2	**1a**	H	H	H	H	B	0	66
3	**1b**	H	Me	H	MeO	A	0	79
4	**1b**	H	Me	H	MeO	B	0	74
5	**1c**	H	HO	H	H	A	37	46
6	**1d**	H	C_5H_{11}	H	MeO	A	0	61
7	**1e**	MeO	H	H	H	A	13	36
8	**1f**	H	MeO	H	H	A	4	44
9	**1g**	H	H	MeO	H	A	36	46
10	**1h**	H	Et_2N	H	H	A	0	10
11	**1i**	MeO	H	Br	H	A	10	57
12	**1j**	Br	H	Cl	H	A	17	51
13	**1k**	H	H	O_2N	H	A	0	47
14	**1l**	Allyl	H	H	H	A	19	61
15	**1m**	Ph	H	H	H	A	23	44

[a] Conditions A: senecialdehyde (1.0 equiv), Et_3N (0.5 equiv), 55 °C, 2.5 d; conditions B: senecialdehyde (1.0 equiv), benzoic acid (0.3 equiv), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanoltrimethylsilyl ether (0.3 equiv), r.t., 3.5 d.
[b] For entries 7–15, see ref. 2a. The ee was determined by HPLC analysis using chiral stationary phases (Daicel Chiralpak AS 0.46 × 25 cm).

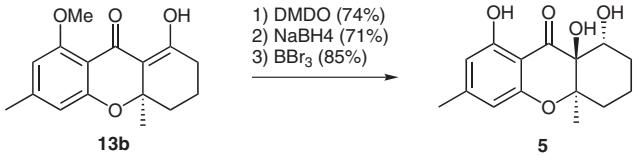
The absolute configuration was determined by correlation with the results of Woggon et al.[3]

Reaction of tricycles **4** with stabilized ylides produced the alcohols **9** as a mixture of the two double-bond isomers (*E*/*Z* ratio between 5:1 and 5:3). Exhaustive concomitant reduction of the double bond and the secondary alcohol[10] led to chromanes **10** in excellent yields.[11] Chromanes **10** were used before by Tietze et al. yielding xanthones **13** through chromanones **12** via a Dieckmann condensation.[5,12] We obtained chromanones **12** by oxidation of the alcohols **9** (Dess–Martin periodinane, DMP) and subsequent hydrogenation. The heterocycles **12** were then cyclized to give xanthones **13** in the presence of titanium tetrachloride (Scheme 2).[5]

Tietze et al. previously converted compound **13b** (which was synthesized starting from orcinol in 12 steps and an overall yield of 14%) into 4-dehydroxydiversonol (Scheme 3).[5]

Starting from orcinol we have shown in this paper that the synthesis of xanthone **13b** could be improved to an eight-step synthesis with an overall yield of 25%.

In conclusion, we have shown that tetrahydroxanthones can be formed from tricycles generated by a vinylogous aldol–oxa-Michael reaction. Furthermore the formal synthesis of 4-dehydroxydiversonol was accomplished.



Scheme 3 Completion of the synthesis of 4-dehydroxydiversonol (**5**) according to Tietze et al.[5]

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(8) **Crystal Structure Study of 4b**
Single-crystal X-ray diffraction studies were carried out on a Nonius KappaCCD diffractometer at 123(2) K using MoK_α radiation ($\lambda = 0.71073$ Å). The structures were solved by Direct Methods (SHELXS-97[13]) and refinement were carried out using SHELXL-97[13] (full-matrix least-squares refinement on F^2). The hydrogen atoms were localized by difference electron density determination and refined using a 'riding' model (H(O)) free).
4b: Colorless crystals, $C_{14}H_{18}O_4$, M = 250.28, crystal size 0.50 x 0.45 x 0.40 mm, triclinic, space group P-1 (No.2): a = 5.9907(2) Å, b = 8.5207(3) Å, c = 12.4965(5) Å, α = 97.603(2)°, β = 95.458(2)°, γ = 97.465(2)°, V = 622.81(4) Å^3, Z = 2, ρ(calcd) = 1.335 Mg m^{-3}, F(000) = 268, μ = 0.097 mm^{-1}, 5344 reflections ($2\theta_{max}$ = 55°), 2715 unique (R_{int} = 0.025), 168 parameters, 1 restraint, R1 ($I > 2\sigma(I)$) = 0.036, wR2 (*all data*) = 0.104, GooF = 1.07, largest diff. peak and hole 0.264 and –0.228 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 717754 (**4b**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(11) **Selected NMR Data**
Compound **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.57 (dd, J = 13.5, 9.8 Hz, 1 H), 1.67 (td, J = 13.5 Hz, 1 H), 2.06–2.14 (m, 2 H), 2.28 (s, 3 H), 3.70 (s, 3 H), 3.86–3.90 (m, 1 H), 4.89 (m_c, 1 H), 5.25 (m_c, 1 H), 6.13 (s, 1 H), 6.24 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 28.6, 34.7, 45.5, 55.4, 61.9, 73.9, 89.9, 102.9, 105.9, 108.5, 140.3, 156.2, 157.1.
Compound **9b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.30 (m, 2 H), 1.28 (t, J = 7.3 Hz, 3 H), 2.04 (s, 3 H), 2.28 (s, 3 H), 2.59 (ddd, J = 14.1, 8.0, 1.3 Hz, 1 H), 2.72 (ddd, J = 14.1, 7.3, 1.3 Hz, 1 H), 3.26 (br s, 1 H), 3.86 (s, 3 H), 4.18 (q, J = 7.3 Hz, 2 H), 4.97 (dd, J = 5.8, 5.3 Hz, 1 H), 5.87 (ddd, J = 15.5, 1.3, 1.3 Hz, 1 H), 6.29 (s, 1 H), 6.35 (s, 1 H), 7.02 (ddd, J = 15.5, 7.8, 7.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 21.7, 25.3, 38.7, 41.4, 55.4, 60.1, 60.2, 75.5, 103.3, 109.9, 111.0, 139.7, 144.4, 153.0, 158.2, 166.3.
Compound **10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H), 1.27 (s, 3 H), 1.53–1.67 (m, 2 H), 1.68–1.85 (m, 4 H), 2.27 (s, 3 H), 2.28–2.34 (m, 2 H), 2.55–2.64 (m, 2 H), 3.80 (s, 3 H), 4.12 (q, J = 7.1 Hz, 2 H), 6.22 (s, 1 H), 6.28 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 16.4, 19.2, 21.6, 23.8, 30.4, 34.5, 38.8, 55.3, 60.2, 75.4, 102.4, 107.0, 110.3, 136.9, 154.1, 157.6, 173.5.
Compound *trans*-**11b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, J = 7.1 Hz, 3 H), 1.39 (s, 3 H), 2.30 (s, 3 H), 2.50–2.74 (m, 4 H), 3.88 (s, 3 H), 4.18 (q, J = 7.1 Hz, 2 H), 5.87 (d, J = 15.5 Hz, 1 H), 6.30 (s, 1 H), 6.37 (s, 1 H), 6.95 (ddd, J = 15.5, 7.6, 7.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.4, 23.9, 41.9, 48.5, 56.0, 60.4, 79.5, 104.7, 108.4, 110.8, 125.4, 142.1, 147.7, 160.2, 160.8, 165.9, 190.0.
Compound *cis*-**11b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3 H), 1.39 (s, 3 H), 2.30 (s, 3 H), 2.59 (d, J = 16.0 Hz, 1 H), 2.77 (d, J = 16.0 Hz, 1 H), 3.13 (m_c, 2 H), 3.88 (s, 3 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.94 (d, J = 11.7 Hz, 1 H), 6.29 (s, 1 H), 6.32–6.40 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.4, 23.7, 38.3, 48.5, 56.0, 60.0, 79.9, 104.6, 108.5, 110.7, 122.7, 143.0, 147.6, 160.2, 161.0, 166.1, 190.4.

Compound **12b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3 H), 1.36 (s, 3 H), 1.60–1.80 (m, 4 H), 2.25–2.30 (m, 2 H), 2.28 (s, 3 H), 2.56 (d, *J* = 15.8 Hz, 1 H), 2.70 (d, *J* = 15.8 Hz, 1 H), 3.86 (s, 3 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 6.26 (s, 1 H), 6.33 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 19.0, 22.3, 23.5, 34.1, 38.5, 48.6, 56.0, 60.3, 80.0, 104.3, 108.4, 110.7, 147.4, 160.1, 161.2, 173.1, 190.7.
Compound **13b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 1.70–1.82 (m, 1 H), 1.91–2.00 (m, 1 H), 2.00–2.08 (m, 2 H), 2.31 (s, 3 H), 2.37 (dd, *J* = 18.7, 5.9 Hz, 1 H), 2.48 (ddd, *J* = 18.7, 11.6, 6.8 Hz, 1 H), 3.92 (s, 3 H), 6.34 (s, 1 H), 6.35 (s, 1 H), 15.98 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 18.3, 22.4, 25.5, 30.2, 35.9, 56.1, 78.2, 105.4, 108.2, 108.7, 111.2, 147.1, 160.2, 160.6, 180.3, 182.0.

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