A Facile Synthesis of Angularly-Fused 3,4,4a,10b-Tetrahydro-2*H*,5*H*-pyrano[3,2-c][1]benzopyrans by the One-pot Condensation between Salicylaldehydes and Unsaturated Alcohols

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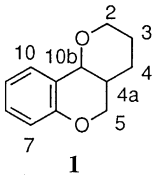
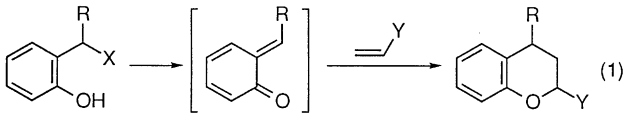
Salicylaldehydes reacted with 5-methyl-4-hexen-1-ol (**4a**) or 6-methyl-5-hepten-2-ol (**4b**) in benzene in the presence of trimethyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid at rt to give angularly-fused *trans*-5,5-dimethyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-pyrano[3,2-c][1]benzopyrans (**6**) in high yields with complete stereoselectivity.

Angularly-fused tetrahydropyrano[3,2-c][1]benzopyran skeletone (**1**) is frequently found in naturally occurring substances, biologically active compounds and others, and efficient methods for their synthesis are highly desired.[1]



1

We previously reported a facile generation and cycloaddition of *o*-quinonemethides (**2**) in aprotic or even protic solvents under very mild conditions (Eq. 1),[2] and we have also recognized that intramolecular cycloadditions of substituted *o*-quinonemethides are highly stereoselective and give a trans-fused tricyclic ring system.[3] We here report a facile stereoselective synthesis of pyranobenzopyrans via intramolecular cycloaddition of presumably formed *o*-quininonemethides possessing unsaturated alkoxy substituent at the methide carbon.

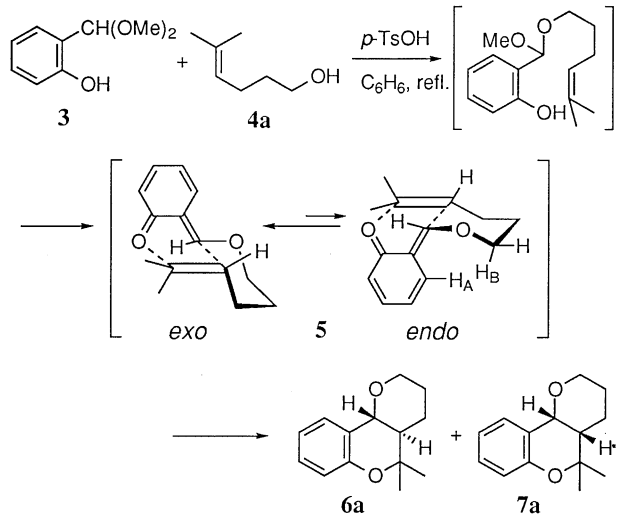


(1)

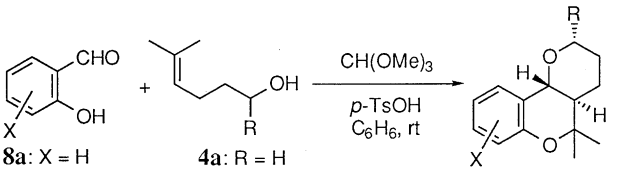
2

At first salicylaldehyde dimethyl acetal (**3**) was heated with 5-methyl-4-hexen-1-ol (**4a**) in benzene in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) at reflux for 1 h to give a 77:23 mixture of *trans*- and *cis*-5,5-dimethyl-3,4,4a,10b-tetrahydro-2*H*,5*H*-pyrano[3,2-c][1]benzopyran (**6a**, **7a**) in 86% yield (Scheme 1). The trans isomer was isolated from the mixture by recrystallization from hexane–ethyl acetate. The structures of the both isomers were determined by MS, IR, ^{1}H- and ^{13}C-NMR spectra, and especially by the NOE experiments in ^{1}H NMR.[4]

To our surprise the formation of the tricyclic compound was observed by simply stirring salicylaldehyde (**8a**), trimethyl orthoformate, 5-methyl-4-hexen-1-ol (**4a**), and a catalytic amount of *p*-TsOH in benzene at rt for 1 h,[5] with rapid *in situ* formation of salicylaldehyde dimethyl acetal, yielding the trans isomer **6a** exclusively in 86% yield. The lack of the orthoformate ester prevented the reaction from going to completion within a reasonable period (Scheme 2).[6]



Scheme 1.



8a: X = H
8b: X = 3-MeO
8c: X = 5-Br
8d: X = 5-NO_2
8e: X = 5,6-CH=CHCH=CH-

4a: R = H
4b: R = Me

6a–h

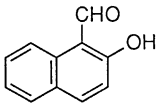
Scheme 2.

A similar cyclization took place using 6-methyl-5-hepten-2-ol (**4b**) as an unsaturated alcohol to give selectively a single stereoisomer **6b** in which B/C ring junction was trans and the methyl was in an equatorial orientation. Formation of trans-fused compounds in these reactions can be understood by noting the steric repulsion between the olefinic hydrogen (H_A) at the 3 position and the axial hydrogen (H_B) at the 3' position of the side chain in the endo transition state (leading to cis-fused compounds) of intramolecular [4 + 2] cycloaddition reaction of substituted *o*-quinonemethide (**5**) (Scheme 1).[7]

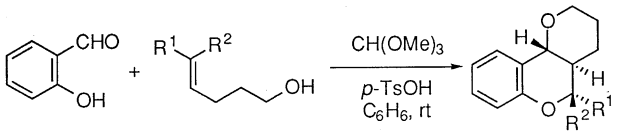
The generality of the present reaction was confirmed using some substituted salicylaldehydes and a related compound: the results are summarized in Table 1.

From synthetic and mechanistic points of view, the stereochemical outcome of the other carbon of the dienophilic olefin moiety is of great interest. Then the reaction of salicylaldehyde with (*E*)- and (*Z*)-5,9-dimethyl-4,8-decadien-1-ol (**9a**, **9b**) was investigated (Scheme 3).

Table 1. Condensation of salicylaldehydes and alcohols[a]

Aldehyde	Alcohol	Time/h	Product	Mp/℃	Yield[b]/%
8a	**4a**	1	**6a**	66–67	86
8a	**4b**	4	**6b**	81–82	96
8b	**4a**	4.5	**6c**	96–97	81
8b	**4b**	1	**6d**	96–98	92
8c	**4a**	1.5	**6e**	liquid	81
8c	**4b**	1	**6f**	95.5-97.5	89
8d	**4a**	8	**6g**	112–114	60
 **8e**	**4a**	4	**6h**	112–114	79

[a] All the reactions were carried out in benzene at rt. [b] Based on isolated pruducts after purification.



9a, 9b **10a, 10b**

a: $R^1 = Me_2C{=}CHCH_2CH_2$, $R^2 = Me$
b: $R^1 = Me$, $R^2 = Me_2C{=}CHCH_2CH_2$

Scheme 3.

A mixture of salicylaldehyde, trimethyl orthoformate, **9a**, and *p*-TsOH was stirred in benzene at rt for 1.5 h to give a single product in 89% yield whose structure was determined by the NMR experiments to be **10a**. Quite similarly the reaction of **8a** with **9b** (87% purity as a mixture with **9a**) under the same reaction conditions afforded stereochemically isomeric **10b** (as 87:13 mixture with **10a**). These facts indicate that the geometry around the olefinic bond is completely retained throughout the reaction.

In summary, an expedient method for the stereoselective synthesis of trans-fused tetrahydropyrano[3,2-c][1]benzopyrans was established by reacting salicylaldehydes with 4-alken-1-ols at rt in the presence of trimethyl orthoformate and a catalytic amount of *p*-TsOH in benzene.

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References and Notes

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3 For reviews of *o*-quinonemethides in the Diels-Alder reaction, see: D. L. Boger and S. M. Weinreb, "Hetero Diels-Alder Methodology in Organic Synthesis," Academic Press, Inc., New York, NY (1987), Chap. 7, p 167; F. Fringuelli and A. Taticchi, "Dienes in the Diels-Alder Reaction," John Wiley & Sons, Inc., New York, NY (1990), Chap. 3, p 125.

4 Spectral data of selected compounds are as follows. **6a**: IR (KBr) 3080, 3050, 2990, 2950, 2850, 1615, 1580, 1480, 1460, 1260, 1135, 1100, 1080, 935, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.20 (s, 3H, Me^{ax}), 1.26–1.41 (m, 1H, 4a-H), 1.39 (s, 3H, Me^{eq}), 1.67–1.83 (m, 3H, 3-H_2, 4-H^{eq}), 1.93 (bd, *J*=12.2, 1H, 4-H^{ax}), 3.60–3.70 (m, 1H, 2-H^{ax}), 4.12–4.19 (m, 1H, 2-H^{eq}), 4.19 (d, *J*=10.6 Hz, 1H, 10b-H), 6.75 (d, *J*=8.2 Hz, 1H, 7-H), 6.89 (t, *J*=7.6 Hz, 1H, 9-H), 7.15 (dd, *J*=8.2, 7.6 Hz, 1H, 8-H), 7.41 (d, *J*=7.6 Hz, 1H, 10-H); ^{13}C NMR ($CDCl_3$) δ 20.38, 25.07, 26.24, 27.55, 45.07, 68.23, 73.55, 78.29, 116.66, 119.87, 122.50, 125.97, 128.77, 152.69. **6b**: IR (KBr) 3060, 2990, 2950, 2870, 1615, 1590, 1490, 1460, 1375, 1310, 1270, 1100, 1085, 955, 940, 760 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.19 (s, 3H, 5-Me^{ax}), 1.30 (d, *J*=6.3 Hz, 3H, 2-Me), 1.33–1.45 (m, 1H, 4a-H), 1.39 (s, 3H, 5-Me^{eq}), 1.53–1.93 (m, 4H, 3-H_2, 4-H_2), 3.65–3.76 (m, 1H, 2-H^{ax}), 4.25 (d, *J*=10.6 Hz, 1H, 10b-H), 6.77 (d, *J*=8.2 Hz, 1H, 7-H), 6.89 (t, *J*=7.6 Hz, 1H, 9-H), 7.14 (dd, *J*=8.2, 7.6 Hz, 1H, 8-H), 7.46 (d, *J*=7.6 Hz, 1H, 10-H). **6h**: IR (KBr) 3080, 2950, 2875, 1620, 1595, 1380, 1235, 1205, 1135, 1060, 930, 810, 750. ^1H NMR ($CDCl_3$) δ 1.16 (s, 3H), 1.37–1.53 (m, 1H), 1.45 (s, 3H), 1.80–2.09 (m, 4H), 3.80–3.90 (m, 1H), 4.22 (bd, *J*=10.0 Hz, 1H), 4.61 (d, *J*=9.6 Hz, 1H), 6.98 (d, *J*=8.9 Hz, 1H), 7.30 (t, *J*=7.9, 1H), 7.45 (t, J=8.2 Hz, 1H), 7.66 (d, *J*=8.9 Hz, 1H), 7.71 (d, *J*=7.9 Hz, 1H), 8.20 (d, *J*=8.2 Hz, 1H).

5 A typical experimental procedure is as follows: A solution of salicylaldehyde (122 mg, 1.0 mmol), 5-methyl-4-hexen-1-ol (**4a**) (137 mg, 1.2 mmol), trimethyl orthoformate (127 mg, 1.2 mmol), and *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol) in benzene (10 ml) was stirred at rt for 1 h. The reaction mixture was neutralized with aqueous sodium hydrogen carbonate, and extracted with ethyl acetate. Purification of the crude product by silica gel column with hexane–ethyl acetate (5%) as eluent afforded **6a** (188 mg, 86%).

6 When a mixture of salicylaldehyde (1.0 mmol), **4a** (1.2 mmol), and *p*-TsOH (0.2 mmol) was heated in benzene at reflux for 4 h, the tricyclic product was obtained in 87% yield, but the product was a mixture of **6a** and **7a** in 72:28.

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