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HIGHLY REGIOSELECTIVE LACTONE FORMATION CATALYZED BY RUTHENIUM COMPLEXES. AN APPLICATION TO SYNTHESIS OF ARYLNAPHTHALENE LIGNANS

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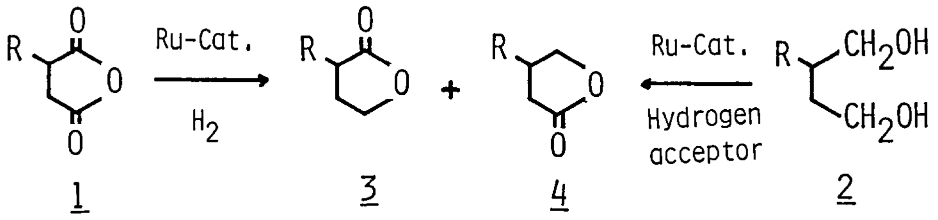
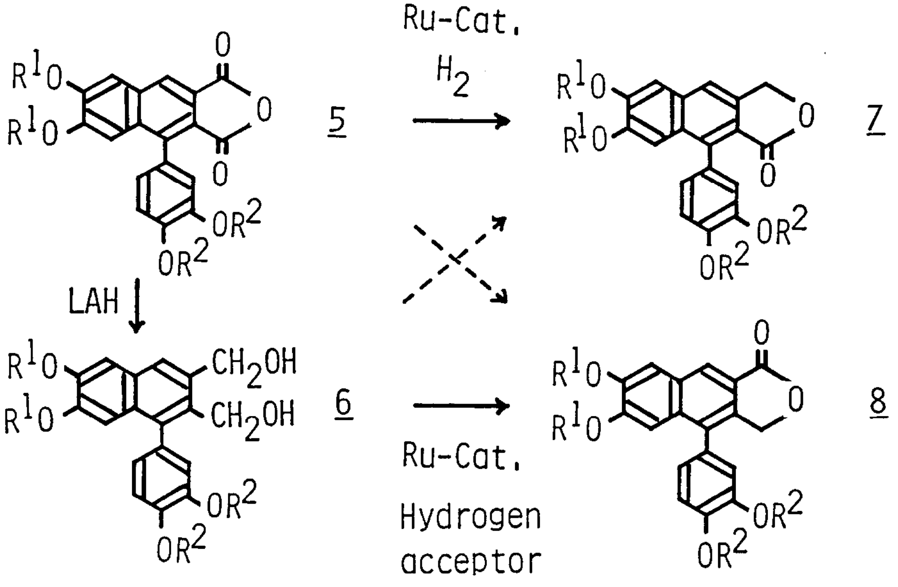
Summary: Ruthenium catalyzed hydrogenation of cyclic anhydrides and dehydrogenation of diols have been successfully applied to the highly regioselective synthesis of arylnaphthalene lignans.

Ruthenium catalyzed hydrogenation of a cyclic anhydride and dehydrogenation of a diol are among promising synthetic methods of lactones. An important feature of these reactions is their high regioselectivities (Eq. 1). The major factor controlling the regioselectivities of these reactions is the steric hindrance effected by the substituents of a substrate. Thus, the hydrogenation of an anhydride 1 affords the lactone 3,$^{1)}$ while the dehydrogenation of an diol 2 affords the lactone 4 predominantly.$^{2)}$ Taking into consideration that 2 is easily obtained by the LAH reduction of 1, the preferential synthesis of either of the lactone isomers 3 and 4 can be realized.



(1)

Here we wish to report the successful application of ruthenium catalyzed hydrogenation of anhydrides 5a-c and dehydrogenation of diols 6a-c to the preferential syntheses of arylnaphthalene lignans 7a-c and 8a-c, which constitute a distinct class of lignans (Eq. 2). The preparation of 5 and 6 is



(2)

a : $R^1 = CH_3$; $R^2 = CH_3$
b : $R^1 = -CH_2-$; $R^2 = CH_3$
c : $R^1 = -CH_2-$; $R^2 = -CH_2-$

well established so that the reduction of 5 and the oxidation of 6 are, though conventional, still potential routes to the arylnaphthalene lignans.[3)] However, most methods appeared in literature transforming 5 or 6 to lignans 7 or 8 are not so effective. $LiAlH(^tBuO)_3$ reduction of 5 is not regioselective enough,[4)] while oxidation of 6 with silver carbonate-Celite (Fetizon's reagent) has suffered from the low chemical yields, in spite that it showed moderate regioselectivity.[5)] Very recently Takano and co-workers reported an improved selective synthesis of 7 and 8 from 5.[6)]

When a toluene solution (20ml) of 5a (2mmol), containing $Ru_2Cl_4(dppb)_3$ (dppb = 1,4-bis(diphenylphosphino)butane, 0.04mmol), PPh_3 (0.2mmol), NEt_3 (0.1ml), and $MgSO_4$ (1g) was heated and stirred at 160°C under H_2 ($15kgw/cm^2$) for 24 h, 7a (dehydrodimethylretrodendrin[4,5)]) was isolated in 88% yield after silica-gel column chromatography and recrystallization. The ratio of lactone isomers 7a:8a was determined to be better than 99:1 on the basis of the relative peak areas for the lactone methylene signals in 400MHz ^1H NMR spectra of the crude reaction mixture. In a similar manner, the hydrogenation of 5b and 5c gave 7b (chinensin[7)]) in 89% and 7c (taiwanin C[8)]) in 82%, respectively.

Table I. Regioselective Hydrogenation of Anhydride 5a

Catalyst[a)]	Time (h)	Yield of 7a (%)	7a : 8a[b)]	Recovery of 5a (%)
$RuCl_2(PPh_3)_3$	24	12	>99 : 1	60
$RuH_2(PPh_3)_4$	24	28	93 : 7	49
$Ru_2Cl_4(dppb)_3$	24	88	>99 : 1	-
$RuH_2(PMe_2Ph)_4$	72	52 (18)[c)]	68 : 32	-

a) 4 mol % as Ru atom. b) Determined by 400MHz ^{1}H NMR measurements.
c) Yield of 8a.

The ratios of lactone isomers 7b:8b and 7c:8c were also better than 99:1. $RuCl_2(PPh_3)_3$, $RuH_2(PPh_3)_4$, and $RuH_2(PMe_2Ph)_4$ were inferior catalysts from the viewpoint of chemical yield and regioselectivity (Table I).

On the other hand, when a toluene solution (10ml) of 6a (2mmol) and benzalacetone (hydrogen acceptor, 4mmol) was refluxed for 10h in the presence of $RuH_2(PPh_3)_4$ (0.08mmol), 8a (dehydrodimethylconidendrin[4,5]) was isolated in 88% yield after the removal of benzylacetone under reduced pressure, column chromatography, and recrystallization. The ratio 7a:8a in the crude reaction mixture was determined to be better than 2:98 by 400MHz ^{1}H NMR measurement. The dehydrogenation of 6b and 6c gave, in a similar manner, 8b (retrochinensin[9]) in 94% and 8c (justicidin E[8b,10]) in 84% yield, respectively.[11] The ratios 7b:8b and 7c:8c were also better than 2:98.

It is supposed that the regioselectivity in the hydrogenation of 5 and the dehydrogenation of 6 is controlled through the steric repulsive effects of aryl group at the 1 position of naphthalene moiety. Both in the hydrogenation of 5 and in the dehydrogenation of 6, the ruthenium catalyst interacts selectively with the functional groups at the less hindered 3 position, which undergo the respective chemical transformation. Conclusively, the ruthenium catalyzed hydrogenation of an anhydride and dehydrogenation of a diol are highly effective methods for the selective syntheses of the arylnaphthalene lignans.

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11) All lignans obtained here gave satisfactory melting points and MS, IR, UV, and ^{1}H NMR spectra. Selected physical data are as follows:

Dehydrodimethylretrodendrin 7a : mp 259-260°C; IR (KBr) 1755cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) δ 5.39 (2s, lactone methylene); MS m/e 381 (M+1$^+$).

Chinensin 7b : mp 224-225°C; IR (KBr) 1760cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) δ 5.37 (2s, lactone methylene); MS m/e 365 (M+1$^+$).

Taiwanin C 7c : mp 255-258°C; IR (KBr) 1765cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) δ 5.37 (2s, lactone methylene); MS m/e 349 (M+1$^+$).

Dehydrodimethylconidendrin 8a : mp 226-228°C; IR (KBr) 1775cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) δ 5.26, 5.21 (AB signal, J=15.0Hz, lactone methylene); MS m/e 381 (M+1$^+$).

Retrochinensin 8b : mp 233-235°C; IR (KBr) 1760cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) δ 5.19, 5.22 (AB signal, J=15.0Hz, lactone methylene); MS m/e 365 (M+1$^+$).

Justicidin E 8c : mp 270-272°C; IR (KBr) 1760cm^{-1} (CO); ^{1}H NMR δ 5.19, 5.21 (AB signal, J=15.0Hz, lactone methylene); MS m/e 349 (M+1$^+$).

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