Tetrahedron Letters,Vol.27,No.12,pp 1339-1342,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain 

# SYNTHETIC STUDIES TOWARD ANTITUMOR QUASSINOIDS. 2.[1]
## A CHIRAL APPROACH TO QUASSIMARIN VIA INTRAMOLECULAR DIELS-ALDER REACTION

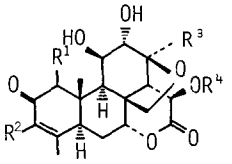
Kozo Shishido[a], Kazuyuki Takahashi[a], Yoshihisa Oshio[a], Keiichiro Fukumoto[a*], Tetsuji Kametani[b], and Toshio Honda[b]

a Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

b Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

**Abstracts:** A tricyclic synthon (**9h**) for quassimarin was synthesized in an optically active form from L-(+)-diethyl tartrate via endo-selective intramolecular Diels-Alder reaction.

Quassimarin (**1**)[2] and bruceantin (**2**)[3] have attracted considerable interest from synthetic chemists because of their biological profiles as potent antitumor agents, as well as their intriguing chemical structures. Although several excellent synthetic approaches to the both quassinoids have been reported[4,5], none of the total synthesis can be achieved so far.

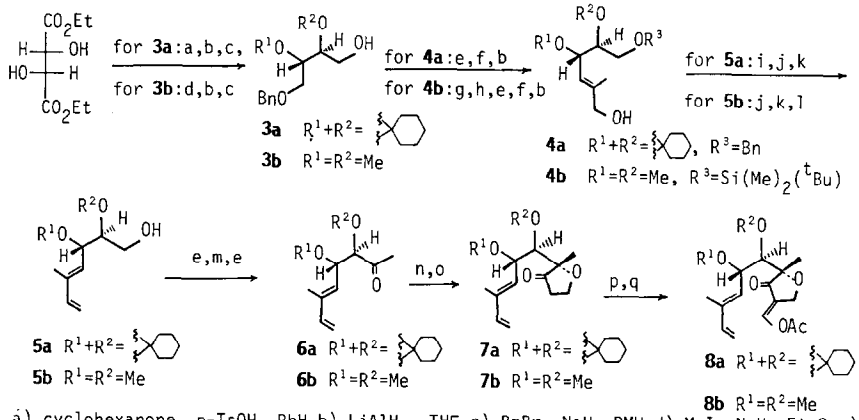


(**1**): $R^1$=OH, $R^2$=H, $R^3$=Me, $R^4$=CO(OAc)(Me)Et

(**2**): $R^1$=H, $R^2$=OH, $R^3$=$CO_2$Me, $R^4$=COCH=C(Me)($^i$Pr)

In the previous publications[1] we reported a stereoselective synthesis of the pentacyclic system as a model for bruceantin in which the key step is the intramolecular Diels-Alder reaction utilizing o-quinodimethane as the diene component. We report here the extension of this methodology to the synthesis of tricyclic chiral synthon for the total synthesis of quassimarin. A recent communication by Schlessinger and Springer[5] on the synthesis of tricyclic synthon for quassimarin via exo-selective intramolecular Diels-Alder reaction has prompted us to report our own efforts in this area.

From the economical point of view, we started from L-(+)-diethyl tartrate which would finally be transformed into the enantiomer of quassimarin. Two trienes, the rigid one (**8a**) and the flexible one (**8b**) were synthesized for comparison of stereoselectivity in the intramolecular Diels-Alder reaction. Sequential Swern oxidation, Wittig reaction, and lithium aluminum hydride reduction of the half benzyl ether (**3a**)[6] gave the allyl alcohol (**4a**) as a mixture of E and Z isomer in a ratio 12 : 1 in 84 % yield. After protection of allylic alcohol moiety in **4a** as alkoxide, benzyl ether was cleaved by Birch reduction to afford the corresponding diol which was then oxidized with acti-

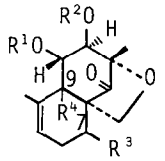


a) cyclohexanone, p-TsOH, PhH b) $LiAlH_4$, THF c) BnBr, NaH, DMH d) MeI, NaH, $Et_2O$ e) Swern ox. f) $Ph_3P{=}C(Me)CO_2Me$, PhH g) $(^tBu)(Me)_2SiCl$, imidazole, $CH_2Cl_2$ h) Li, liq.$NH_3$ i) NaH, THF then Li, liq.$NH_3$ j) $MnO_2$, $CH_2Cl_2$ k) $Ph_3PMeBr$, $^n$BuLi, THF l) $^nBu_4NF$ m) MeLi, $Et_2O$ n) α-methoxyallene, $^n$BuLi, $MgBr_2$, THF o) $^t$BuOK, $^t$BuOH then HCl p) $HCO_2Et$, NaH, DME q) $Ac_2O$, py., 4-DMAP, $CH_2Cl_2$

Scheme 1

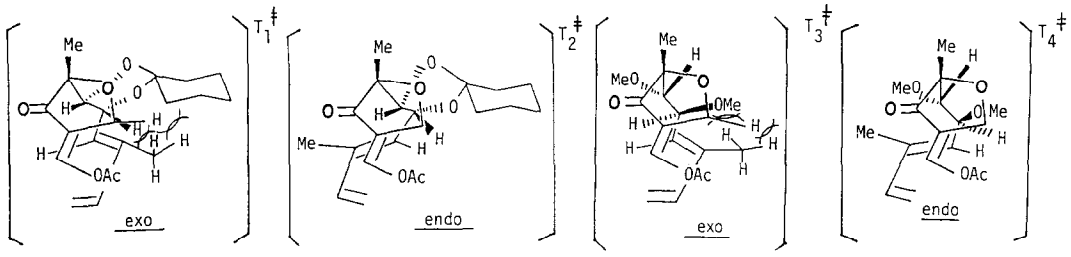
vated manganese oxide followed by Wittig olefination to furnish the dienol (**5a**) in 65 % yield. On the other hand, in the case of (**3b**)[7], the same sequence for the conversion could not be used because of the lower yield(39 %) at the stage of oxidation of the diol with manganese oxide. After silylation and Birch reduction of **3b**, the corresponding alcohol was treated with the same procedures as for **3a** to provide a 14 : 1 mixture of the isomeric allyl alcohol in 67 % yield from **3b**. The structure of major isomer could be comfirmed as **4b** by $^1$HNMR n.O.e. Sequential treatment of **4b** with manganese oxide, methylenetriphenylphosphorane, and tetrabutylammonium fluoride gave the dienol (**5b**) in 79 % yield. Swern oxidation of **5a** and **5b** generated the aldehydes which, without isolation, were further reacted with methyllithium followed by Swern oxidation to afford the methyl ketones (**6a**) and (**6b**). The key stereoselective construction of the dihydrofuranone moiety was achieved via $Mg^{2+}$ ion controlled addition [8] of α-methoxyallene to α, β-dialkoxy ketone. Thus, treatment of (**6a**) and (**6b**) with α-lithio-α-methoxyallene[9,10], generated in situ from methoxyallene with n-butyllithium, in the presence of magnesium bromide followed by acidic hydrolysis of the resulting methyl enol ether afforded exclusively the desired dihydrofuranones (**7a**) and (**7b**)[11,12] in 16 % and 67 % yield from the secondary alcohols, respectively (via Cram-cyclic model). In the conversion, the addition of allenyl anion to **6b** without magnesium bromide resulted in the generation of diastereomeric mixture in a ratio of 4 : 6 (from $^1$HNMR), the predominant isomer was the undesired one (via Cram-Felkin model). Introduction of the dienophile portion into an α-position of the ketone in **7a** and **7b** was accomplished by sequential formylaiton and acetylation. Having the key trienes (**8a**) and (**8b**)[13] in hand, the construction of tricyclic synthon for quassimarin now depended on a crucial intramolecular Diels-Alder reaction. Thermolysis[14] of **8a** (xylene solution, 180°C, 53 h, sealed tube) followed by basic hydrolysis (LiOH, aq. MeOH) of the resulting acetate gave two isomeric

alcohols in 18 % and 7 % yield, respectively. Both alcohols were then independently converted to the acetate (**9a**)[15] and (**9c**)[16], which were characterized by 400 MHz $^1$HNMR spectrum. The structure of the major adduct (**9a**) was further confirmed by X-ray crystallographic analysis. On the other hand, thermolysis of **8b**[14] (toluene solution, 150°C, 1 h, sealed tube) proceeded smoothly to give the adduct which was hydrolyzed (LiOH, aq. MeOH) to furnish the alcohol (**9f**)[17], whose structure was confirmed by X-ray analysis, along with a trace amount of the isomeric alcohol (**10**)[18] via the exo-transition state ($T_3$) in a ratio of >30 : 1 in 85 % yield. From these results, it was found that the intramolecular Diels-Alder reactions of **8a** and **8b** proceeded in a highly endo-selective manner which could be rationalized by considering the transition states(for **8a** : $T_1^{\ddagger} < T_2^{\ddagger}$, for **8b** : $T_3^{\ddagger} < T_4^{\ddagger}$).



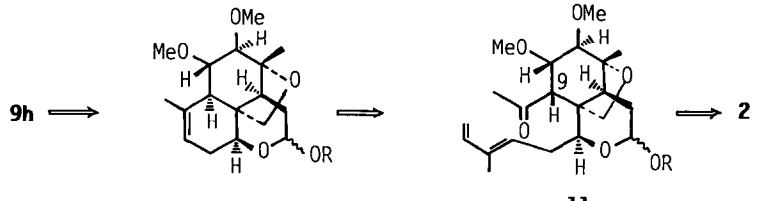
**9a** $R^1+R^2=$  , $R^3=\alpha$-OAc, $R^4=\alpha$-H
**b** " , $R^3=\alpha$-OH, $R^4=\alpha$-H
**c** " , $R^3=\beta$-OAc, $R^4=\alpha$-H
**d** " , $R^3=\beta$-OH, $R^4=\beta$-H
**e** $R^1=R^2=$Me, $R^3=\alpha$-OAc, $R^4=\alpha$-H
**f** " , $R^3=\alpha$-OH, $R^4=\alpha$-H
**g** " , $R^3=\alpha$-$OSO_2$Me, $R^4=\alpha$-H
**h** " , $R^3=\beta$-OAc, $R^4=\alpha$-H

**10** $R^1=R^2=$Me, $R^3=\alpha$-OH, $R^4=\beta$-H




Attempted inversion of the configuration at the future C-7 in **9f** proved to be successful by treating the corresponding mesylate (**9g**) with cesium acetate in the presence of 18-crown-6[19] affording the inverted acetate (**9h**)[20] in 45 % yield.

In our remaining synthetic strategy for quassimarin (Scheme 2), the undesired configuration at the future C-9 in **9h** would be epimerizable via the methyl ketone intermediate (**11**).




**11**

Scheme 2

Further studies along this line are in progress.

**REFERENCES AND NOTES**


1) K. Shishido, T. Saitoh, K. Fukumoto, and T. Kametani, J. Chem. Soc. Chem. Commun., **1983**, 852; idem, J. Chem. Soc. Perkin I, **1984**, 2139.
2) S. M. Kupchan and D. R. Streelman, J. Org. Chem., **41**, 3481 (1976).
3) S. M. Kupchan, R. W. Britton, M. F. Ziegler, and C. W. Siegel, J. Org. Chem., **38**, 178 (1973).
4) F. E. Ziegler, S. I. Klein, U. K. Pati, and T.-F. Wang, J. Am. Chem. Soc., **107**, 2730 (1985), and the references cited therein.
5) R. H. Schlessinger, J.-W. Wong, M. A. Poss, and J. P. Springer, J. Org. Chem., **50**, 3950 (1985), and the references cited therein.
6) T. Mukaiyama, Y. Goto, and S. Shoda, Chem. Lett., **1983**, 671.
7) I. Felner and K. Schenker, Helv. Chim. Acta, **53**, 754 (1970).
8) K. Mead and T. L. Macdonald, J. Org. Chem., **50**, 422 (1985).
9) D. Gange and P. Magnus, J. Am. Chem. Soc., **100**, 7746 (1978).
10) For a Cram-cyclic diastereoselective addition of α-lthio-α-methoxyallene, see L. E. Overman and S. W. Goldstein, J. Am. Chem. Soc., **106**, 5360 (1984).
11) The configuration at newly formed quaternary center could not be determined at this stage, and it was firmly established by the eventual conversion of **7a** and **7b** to **9a** and **9f**.
12) **7a** : $[\alpha]_D$ -66.7° (c=1.29, $CHCl_3$); mp 83-85°C (ether-$^n$hexane); IR($CHCl_3$): 1755 $cm^{-1}$. **7b** : $[\alpha]_D$ +114.4°(c=0.82, $CHCl_3$); IR($CHCl_3$): ν 1750 $cm^{-1}$.
13) The configuration of the dienophile enone in **8a** and **8b** was homogeneous from $^1$HNMR and was assigned as "E". Chemical shift of the β-proton of the enone, for **8a**; δ ($CDCl_3$) 8.33, for **8b**; δ ($CDCl_3$) 8.07.
14) Although the Lewis acid [$Et_2AlCl$, $TiCl_4$, or $BF_3$ $OEt_2$] catalyzed cycloaddition was also examined under various conditions, no cycloadducts could be obtained.
15) $[\alpha]_D$-196.0°(c=0.79, $CHCl_3$); mp 154-156°C(ether-$^n$hexane).
16) The occurrence of an epimerization at the future C-7 might be explainable by equilibration via retro Diels-Alder reaction and readdition under such considerable harsher thermal condition (at 180°C for 53 h). cf.) K. Shishido, K. Hiroya, Y. Ueno, K. Fukumoto, T. Kametani, and T. Honda, Chem. Lett., **1984**, 1653.
17) $[\alpha]_D$-116.7°(c=1.02, $CHCl_3$); mp 147-148°C(ether-$^n$hexane).
18) For the acetate of **10**, $[\alpha]_D$-140.1°(c=0.70, $CHCl_3$); IR($CHCl_3$): 1720, 1770 $cm^{-1}$; $^1$HNMR($CDCl_3$, 100 MHz): δ 1.32(3H, s), 1.72(3H, br s), 2.00(3H, s), 3.40(3H, s), 3.42(3H,s), 4.08(1H, dd, J=2, 8 Hz), 4.56(1H, d, J=8 Hz), 5.14(1H, m), 5.40(1H, m); MS(m/z): 324($M^+$).
19) Y. Torisawa, H. Okabe, and S. Ikegami, Chem. Lett., **1984**, 1555.
20) $[\alpha]_D$ -83.0°(c=1.54, $CHCl_3$); $^1$HNMR($CDCl_3$, 100 MHz): δ 4.94(1H, dd, J=9.5, 9 Hz).


(Received in Japan 21 January 1986)