Tetrahedron Letters, Vol. 33, No. 24, pp. 3527-3530, 1992
Printed in Great Britain

0040-4039/92 $5.00 + .00
Pergamon Press Ltd

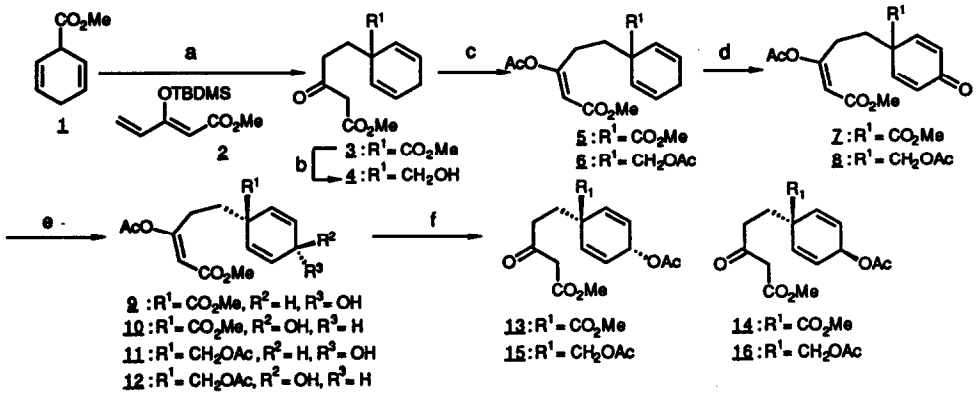
SYNTHESIS OF *cis*-DECALIN DERIVATIVE VIA π-ALLYLPALLADIUM INTERMEDIATE AND ITS TRANSFORMATION TO USEFULLY FUNCTIONALIZED *trans*-DECALIN DERIVATIVE

Toshiyasu Takemoto,[a] Yuji Nishikimi,[b] Mikiko Sodeoka,[b] and Masakatsu Shibasaki[a]*

[a]Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan
[b]Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

Abstract: **Treatment of 15 or 16 with $Pd(PPh_3)_4$ (10 mol %) and NaH (1.2 equiv) afforded the *cis*-decalin derivative 18 stereoselectively in high yield, which was effectively transformed into the usefully functionalized *trans*-decalin derivative 29.**

The discovery of new methods for the asymmetric construction of usefully functionalized decalin derivatives continues to be a current research objective, because decalin skeletons are found in many bioactive molecules such as steroids, aphidicolin and azadirachtin. In this communication, we report an effective synthesis of the *cis*-decalin derivatives **17** and **18** starting with the prochiral substrates **13**, **14**, **15** and **16**, which is applicable to a catalytic asymmetric synthesis.[1] Moreover, transformation of **18** to the usefully functionalized *trans*-decalin derivative **29** is also described.



Scheme 1. a) LDA, THF, HMPA, -78 °C, 0.5 hr ; 2, TMSCl, THF, -78 °C, 2 hr ; TBAF, AcOH, THF, rt, 1 hr (82%), b) NaH, ether, 0 °C, 0.5 hr; $LiAlH_4$, 0 °C, 1 hr (89%), c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 1 hr (5: 73%, 6: 79%), d) CrO_3 (10 equiv), 3,5-DMP (10 equiv), CH_2Cl_2, -20 °C, 1 hr (7: 54%, 8: 80%), e) $NaBH_4$ (1.5 mol equiv), $CeCl_3 \cdot 7H_2O$ (1.5 mol equiv), MeOH, -30 °C, 1 hr (9: 25%, 10: 44%, 11: 55%, 12: 43%), f) K_2CO_3 (1.2 mol equiv), MeOH, 0 °C, 10 min; Ac_2O (1.0equiv), Et_3N, DMAP,CH_2Cl_2, rt, 15 hr (13: 90%, 14: 75%, 15: 83%, 16: 75%)

The four prochiral substrates **13**, **14**, **15** and **16** for the catalytic synthesis of decalin derivatives were designed on the basis of the following fact. It is well-known that reactions via π-allylpalladium complexes proceed with overall net retention of configuration.[2] Thus, the usefully functionalized decalin derivatives **17** and **18** were expected to be produced from **13** and **15**, respectively, while the corresponding *trans*-isomers were anticipated to be formed from **14** and **16**, respectively. The requisite prochiral substrates for the catalytic synthesis of decalin derivatives were synthesized as follows. Treatment of the ester enolate, generated from **1** and LDA in THF-HMPA, with the silyl enol ether of Nazarov reagent[3] **2** in the presence of trimethylsilyl

chloride[4] afforded a mixture of the Michael adducts, which was immediately converted to the β-keto ester **3** in 82% overall yield on exposure to tetrabutylammonium fluoride and acetic acid. The β-keto ester **3** was then transformed into the *E*-enol acetate **5** stereoselectively[5] (73%), which underwent allylic oxidation by CrO_3 and 3,5-DMP[6] to give **7** in 54% yield. $NaBH_4$ reduction of **7** in the presence of $CeCl_3 \cdot 7H_2O$[7] afforded the α-alcohol **9** (25%) and the β-alcohol **10** (44%),[8] both of which were converted to **13** and **14** in 90% and 75% yields, respectively, by treatment with K_2CO_3 in methanol followed by acetylation. Likewise, **3** was transformed into the prochiral substrates **15** and **16** as follows. After protection of the β-keto ester as a sodium enolate, $LiAlH_4$ reduction gave the alcohol **4** chemoselectively, which was transformed into the enol acetate **6** stereoselectively[5] in 70% overall yield. Allylic oxidation of **6**[6] provided the dienone **8** in 80% yield, which underwent reduction to provide the α-alcohol **11** (55%) and the β-alcohol **12**(43%).[8] Both of the alcohols **11** and **12** were treated with K_2CO_3 in MeOH followed by acetylation, giving the prochiral substrates **15** and **16** in 83% and 75% yields, respectively.

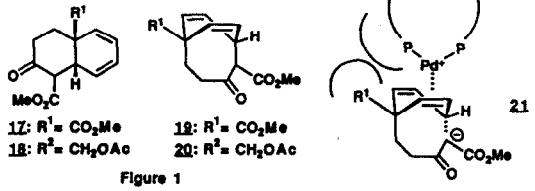


Figure 1

With the four prochiral substrates available, cyclization of **13**, which was expected to lead to the *cis*-decalin derivative **17**, was first investigated. Contrary to expectations, treatment of **13** with $Pd(dba)_2$ (10 mol %), diphenylphosphinoethane (DIPHOS) (20 mol %) and NaH (1.2 equiv) in THF at 50 °C produced only the 8-membered product **19**[9] in 20% yield. After several attempts, it was found that the use of $Pd(PPh_3)_4$ (10 mol %) in CH_3CN instead of $Pd(dba)_2$-DIPHOS gave the desired **17** in 73% yield together with **19** (24%). The same tendency was also observed in the case of **15**. The results are summarized in Table 1. The stereochemistry of the cyclized products **17** and **18** was unequivocally determined by NOE experiments.[10] Exclusive fromation of the 8-membered product **19** (run 1, Table 1) would be ascribed to the smaller cone angle of DIPHOS than that of PPh3.[11] That is, use of a phosphine ligand with relatively small cone angle gives the 8-membered product via the transition state **21**, while use of a phosphine ligand with larger cone angle brings about increased nonbonded repulsion in the transition state **21**, thus producing the *cis*-decalin derivative as the major product. Next, with the aim of synthesizing the corresponding *trans*-decalin derivatives, cyclization of the prochiral substrates **14** and **16** was carried out. In all the cases examined, however, none of the *trans*-decalin derivatives was formed.[12] That is, treatment of **14** with $Pd(dba)_2$-DIPHOS-NaH in THF afforded **17** in 6% yield together with **19** (39%). Furthermore, reaction of **16** with $Pd(PPh_3)_4$-NaH in CH_3CN provided

Table 1. Reaction of 13 or 15 with Pd(0) Catalyst and NaH

substrate	catalyst (10 mol %)	ligand (10 mol %)	solvent	temp. (°C)	product: yield
13	$Pd(dba)_2$	DIPHOS	THF	50	17: — 19: 20%
13	$Pd(PPh_3)_4$	—	THF	0	17: 53% 19: 8%
13	$Pd(PPh_3)_4$	—	CH_3CN	20	17: 73% 19: 24%
15	$Pd(dba)_2$	DIPHOS	THF	70	18: 17% 20: 32%
15	$Pd(PPh_3)_4$	—	THF	20	18: 77% 20: 4%

Table 2. Reaction of 14 or 16 with Pd(0) Catalyst and NaH

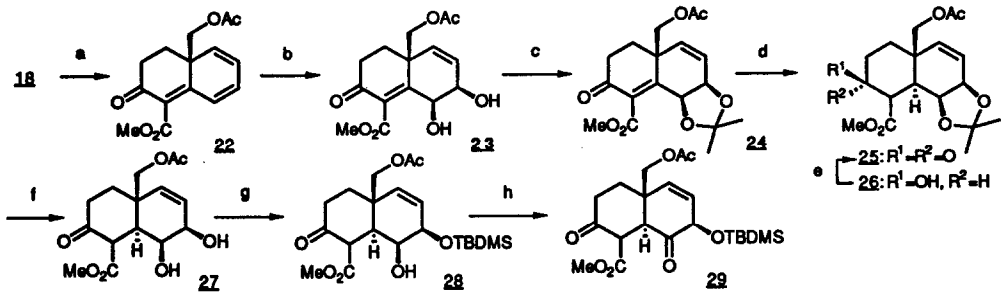
substrate	catalyst (10 mol %)	ligand (10 mol %)	solvent	temp. (°C)	product: yield
14	$Pd(dba)_2$	DIPHOS	THF	50	17: 6% 19: 39%
14	$Pd(PPh_3)_4$	—	CH_3CN	40	17: 60% 19: 14%
16	$Pd(dba)_2$	DIPHOS	THF	70	18: 11% 20: 15%
16	$Pd(PPh_3)_4$	—	CH_3CN	50	18: 79% 20: 7%
16	$Pd(PPh_3)_4$	—	THF	40	18: 17% 20: 4%

18 (79%) and **20** (7%). The results are summarized in Table 2, suggesting that the *cis*-decalin derivative would be formed stereoselectively in high yield even from a mixture of the stereoisomers. In fact, treatment of a mixture of **15** and **16** (1:1) with $Pd(PPh_3)_4$ (10 mol %) and NaH (1.2 equiv) in CH_3CN at 20 °C gave the *cis*-decalin derivative **18** in 96% yield together with **20** (4%). Exclusive formation of the *cis*-decalin derivative reveals that full inversion of configuration of the π-allylpalladium intermediate occurred owing to the difficulty of *trans*-decalin formation. The mechanism of the inversion appears to be Pd(0) (phosphine) displacement of palladium in the π-allylpalladium intermediate because the reaction rate was remarkably accelerated by increasing the concentration of $Pd(PPh_3)_4$ as shown in Table 3.[13]

Table 3. Reaction of 16 with $Pd(PPh_3)_4$ and NaH in CH_3CN at 20 °C under Various Conditions

entry	$Pd(PPh_3)_4$ (mol %)	time (hr)	yield of 18 (%)
1	10	40	7
2	30	23	55
3	60	15	51

Having established an effective synthesis of *cis*-decalin derivatives, transformation of **18** to the usefully functionalized *trans*-decalin **29** was next investigated. The successful result is shown in Scheme 2. The decalin derivative **29** appars to be a potential intermediate for the synthesis of the azadirachtin western part.[15,16]



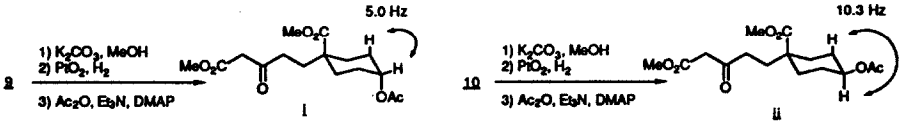
Scheme 2. a) NaH, PhSeBr, THF, 0 °C, 0.5 hr; 30% H_2O_2, CH_2Cl_2, rt, 0.5 hr (22: 48%, 18: 17%) b) OsO_4, ether, pyridine, -78 °C, 0.5 hr; 20% $NaHSO_3$, rt, 0.5 hr, 72% c) 2,2-dimethoxypropane, CSA, CH_2Cl_2, rt, 1 hr, 63% d) $NaBH_4$, pyridine, -30 °C, 0.5 hr (25: 53%, 26: 23%)[14] e) Collins oxid., 75% f) 80% AcOH, 60 °C, 22 hr, 80% g) TBDMSCl, imidazole, DMF, rt, 20 hr, 85% h) PCC, MS-4A, CH_2Cl_2, rt, 14 hr, 75%

In conclusion, we have developed an efficient synthesis of the *cis*-decalin derivatives utilizing the π-allylpalladium chemistry as a key step. Furthermore, **18** has been successfully converted to the usefully functionalized *trans*-decalin derivative **29**. Application to a catalytic asymmetric synthesis of decalin derivatives is discussed in the following paper.

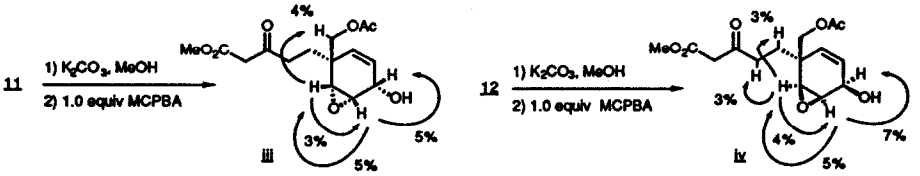
References and Notes

1. The following paper in this issue.
2. G. Consiglio and R. M. Waymouth, *Chem. Rev.*, 89, 257 (1989), and references cited therein.
3. R. Zibuck and J. M. Steiber, *J. Org. Chem.*, 54, 4717 (1989). The silyl enol ether 2 was prepared by treatment with *tert*-butyldimethylsilyl chloride and triethylamine in CH_2Cl_2 (89%).
4. Me_3SiCl was used for the enolate-trap to prevent polymerization. See: (a) N. Slougiand G. Rousseau, *Synth. Commun.*, 17, 1 (1987). (b) C. I. Ainsworth and Y. N. Kuo, *J. Organometal. Chem.*, 46, 73 (1972).
5. The stereochemistry of 5 and 6 was determined from the ^{1}H-NMR spectra, which showed δ 5.67 ppm and 5.94 ppm (vinyl proton), respectively. The ^{1}NMR spectra of the corresponding *Z*-isomer showed δ 5.59 ppm and 5.60 ppm, respectively.
6. W. G. Salmond, M. A. Barta and J. L. Havens, *J. Org. Chem.*, 43, 2057 (1978).
7. A. L. Gemaland and J. L. Luche, *J. Am. Chem. Soc.*, 103, 5454 (1981).

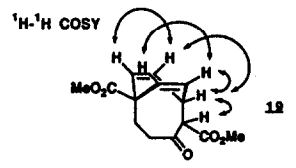
8. The stereochemistry of **9** and **10** was determined from the ^{1}H-NMR coupling constants of **i** and **ii**.



The stereochemistry of **11** and **12** was determined from the NOE experiments as shown below.



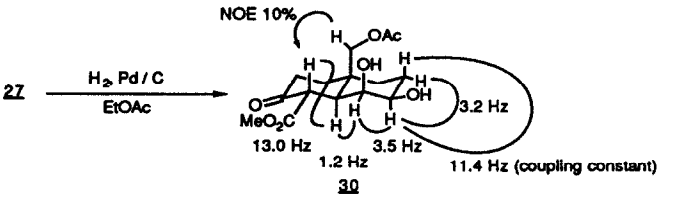
9. ^{1}H-^{1}H COSY



19

^{1}H-NMR ($CDCl_3$) δ 1.89 (m, 2H), 2.41 (ddd, J = 5.8, 5.8, 11.8 Hz, 1H), 2.59 (ddd, J = 5.8, 8.0, 11.8 Hz, 1H), 3.48 (dt, J = 4.1, 5.8 Hz, 1H), 3.76 (s, 6H), 3.79 (d, J = 4.1 Hz, 1H), 6.15 (dd, J = 5.8, 9.7 Hz, 1H), 6.22 (d, J = 9.7 Hz, 2H), 6.39 (dd, J = 5.8, 9.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$) 30.6, 34.5, 37.9, 49.1, 52.3, 52.6, 68.2, 129.4, 129.5, 131.2, 131.6, 169.3, 174.2, 201.2 IR (neat) 1730, 1710 cm^{-1} MS m/z 264 (M^+), 105 (base peak) HR-MS (M^+) calcd for $C_{14}H_{16}O_5$: 264.0998 found : 264.0990 UV (MeOH) λ_{max} 290 nm

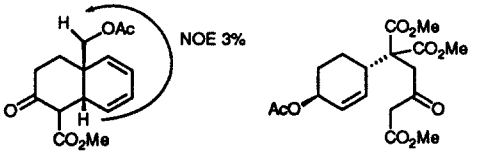
10. **17** was transformed into **18** (i. NaH, $LiAlH_4$, ii. Ac_2O, Et_3N).
11. C. A. Tolman, *Chem. Rev.*, **77**, 313 (1977).
12. In contrast to this result, the β-keto ester **v** afforded a mixture of the *trans*-decalin and the *cis*-decalin (1 : 1). See : J. -E. Bäckvall, J. -O. Vågberg, and K. L. Granberg, *Tetrahedron Lett.*, **30**, 617 (1989).
13. For the inversion of π-allylpalladium complexes, see: (a) T. Takahashi, Y. Jinbo, K. Kitamura, J. Tsuji, *Tetrahedron Lett.*, **25**, 5921 (1984). (b) P. R. Auburn, P. B. Mackenjie, and B. Bosnich, *J. Am. Chem. Soc*, **107**, 2033 (1985). (c) S. Murahashi, Y. Taniguchi, Y. Imada, Y. Tanigawa, *J. Org. Chem.*, **54**, 3292 (1989).
14. W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965).
15. The stereochemistry of **27** was determined as follows.



30

Spectral data for **27** : ^{1}H-NMR (C_6D_6) δ 0.45-0.60 (m, 1H), 0.60-0.65 (m, 1H), 1.20-1.45 (m, 1H), 1.60-1.78 (m, 3H), 1.65 (s, 3H), 1.96 (dd, J = 13.6, 1.2 Hz, 1H), 2.14-2.50 (m, 2H), 3.12 (ddd, J = 11.3, 4.6, 3.1 Hz, 1H), 3.56 (s, 3H), 3.63 (dd, J = 3.1, 1.2 Hz, 1H), 3.86 (d, J = 13.6 Hz, 1H), 4.17 (dd, J = 12.5, 1.3 Hz, 1H), 4.98 (d, J = 12.5 Hz, 1H). IR (neat) 3450, 1730, 1710 cm^{-1} MS m/z 313 (M^+-H), 295(M^+-H-H_2O), 44 (base peak) HR-MS (M^+) calcd for $C_{15}H_{21}O_7$: 313.1287 found : 313.1302

16. For the eastern part of azadiracitin, see: (a) Y. Nishikimi, T. Iimori, M. Sodeoka, M. Shibasaki, *J. Org. Chem.*, **54**, 3354 (1989). (b) J. C. Anderson, S. V. Ley, D. Santafianos, R. N. Sheppard, *Tetrahedron*, **47**, 6813 (1991). For the western part, see: H. C. Koland and S. V. Ley, *Tetrahedron Lett.*, **32**, 6187 (1991).



(Received in Japan 4 March 1992)