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Asymmetric Bridging Annulation Reaction Involving the Intramolecular Conjugate Addition of Chiral Imines to Enoates: Access to a Polycyclic System Related to the Taxane Core

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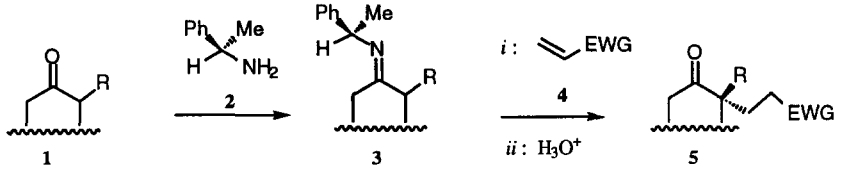
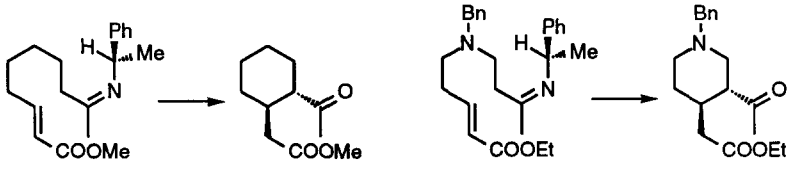
Abstract : (R)-1-phenylethylamine-induced cyclization of ketoenoate 2 4 led to a 2:1 mixture of "all-cis" polycyclic adducts 2 5 and 2 6, structurally related to the taxane series.

Ten years ago, we reported that chiral imines **3**, derived from *racemic* 2-alkylcyclanones **1** and optically active 1-phenylethylamine **2**, add, *under neutral conditions*, to electrophilic alkenes **4** leading, after hydrolytic work-up, to 2,2-dialkylcyclanones **5** with a good yield and excellent regio- and stereoselectivity.[2]



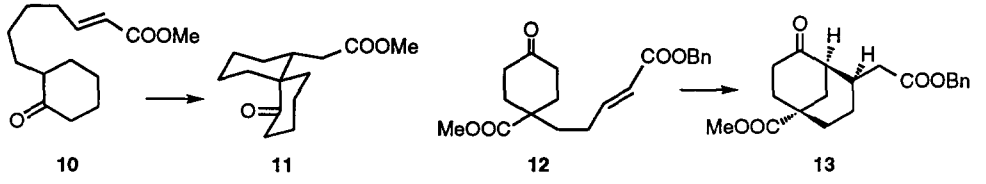
(typical ee: 90-98 %)

This Michael addition, which tolerates a great variation in the nature of the starting cyclanone and the electrophilic alkene, constitutes indisputably one of the most potent methodology for the *enantioselective elaboration of quaternary carbon centers.* In this respect, it has been successfully applied by ourselves and others to the asymmetric synthesis of various compounds of natural origin, including terpenes, steroids and alkaloids.[2] The mechanistic aspects of this reaction have also been extensively investigated, from both experimental and theoretical viewpoints.[2] Several *intramolecular variants* of this Michael addition have been developed; thus, for example, chiral imines **6**[3] and **8**[4] underwent a facile *carbocyclization* under thermal conditions, furnishing, after hydrolytic work-up, derivatives **7** and **9**, respectively, with an excellent enantioselectivity (α 90%).



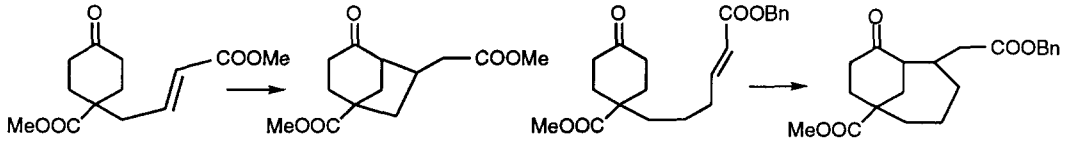
6 **7** **8** **9**

On the other hand, (*R*)-1-phenylethylamine-induced *spiroannulation* of ketoenoate **10** led to ketoester (1*S*, 2*R*)-**11** with a high degree of control (≥ 90%) of the two newly created stereogenic centers.[5] In a similar fashion, *bridging annulation* of ketoenoate **12**, induced by (*ent*)-**2**, gave the bicyclo[3.3.1]nonane derivative **13** with a high level of stereoselectivity (100% de, 90% ee).[6]



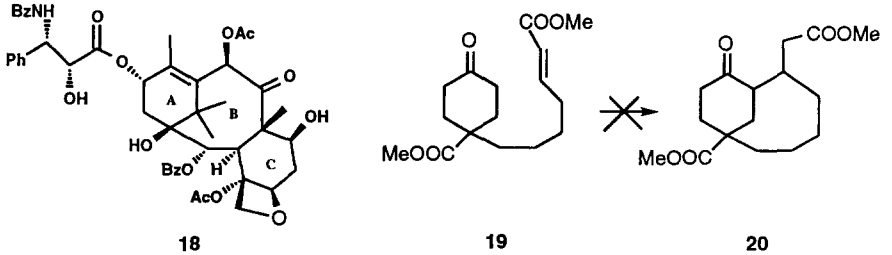
10 **11** **12** **13**

However, this bridging annulation proved to be very sensitive to the size of the newly created ring; thus, the [3.2.1] and [4.3.1] bicyclic compounds **15** and **17**, elaborated from ketoenoates **14** and **16**, respectively, were both obtained with a low degree of stereoselectivity (60% de, 30% ee and 20% de, respectively).[6]



14 **15** **16** **17**

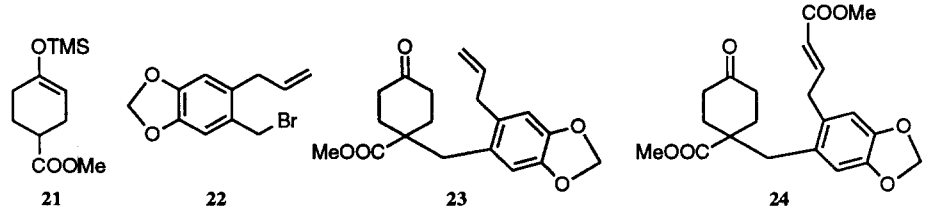
In connection with our synthetic efforts in the taxane series (exemplified by taxol **18**)[7], we recently planed the construction of the [AB] ring framework of these systems, by extending the present bridging annulation. However, all attempts at elaborating the bicyclo[5.3.1]undecane derivative **20** by 1-phenylethylamine-induced cyclization of ketoenoate **19** were invariably unsuccessful, a reflect of the difficulties usually encountered in establishing eight-membered carbocycles from open-chain precursors.[6]



18 **19** **20**

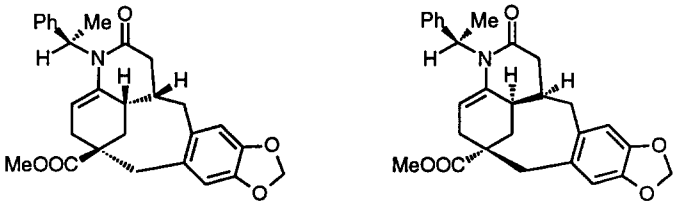
In light of the preceding observation, we reasoned that the intercalation of an aromatic moiety, precursor of the future C ring of taxanes, in the side-chain of **19**, by reducing significantly the degrees of freedom of the system, as well as the transannular strain in the eight-membered adduct, would favor the annulation reaction.[8] This was tested on model ketoenoate **24**, efficiently elaborated by condensing first the lithio derivative of ester **21**[9] with bromomethylsafrole **22**[10] (*i* : **21**, 1.5 eq of LDA, THF, 30 min at -78 °C; *ii* : **22**, -78 °C→20 °C, then 12 h at this temperature; *iii* : 1N HCl, 1 h at 20 °C). Compound **23**, thus obtained with a 58% overall yield, was

then converted into ketoenoate **24**[11] through a two-step sequence (*i* : *cat* OsO_4, $NaIO_4$, Et_2O, H_2O, 1 h at 20 °C; *ii* : Ph_3P=CH-COOMe, CH_2Cl_2, 24 h at 20 °C, 70 % overall yield).



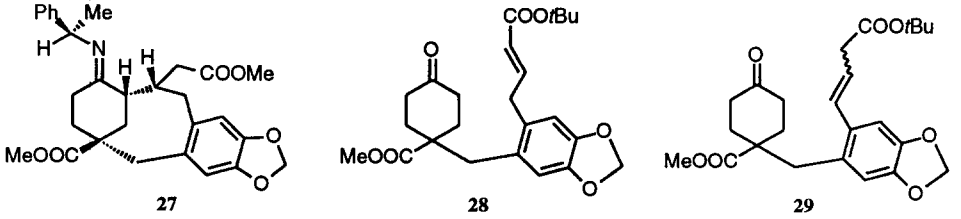
21 **22** **23** **24**

Ketoenoate **24** was then cyclized [2 eq of (*R*)-1-phenylethylamine, 72 h in refluxing toluene, with removal of water], leading with a 48 % yield to a 2:1 mixture of isomeric adducts **25**[12] and **26**[13], respectively. These were separated by preparative HPLC[14] and fully characterized. The same "*all-cis*" relative stereochemistry in the tricyclic systems of **25** and **26** was established through the complete assignments of the ^1H and ^{13}C NMR resonances, including 1D and 2D experiments, PFG-phase sensitive DQF COSY, and ^1H-^{13}C direct and long range correlations (PFG-HMQC and PFG-HMBC). The proposed absolute configurations of the three newly created stereogenic centers in **25** and **26**, although not definitively established, rests on the mechanism of the present Michael addition, assuming that the addition took place predominantly on the less hindered side of the intermediary chiral imine, *anti* to the phenyl group of the inducer.[2,6]



25 **26**

It is clear that the formation of adducts **25** and **26** from **24** involves the intermediary Michael adducts (*e.g.* **27**) which underwent a lactamization side-reaction. In order to minimize such a lactamization process, 1-phenylethylamine-induced cyclization of ketoenoate **28**, the *tert*-butyl ester analog of **24**, was next investigated. However, when **28** was submitted to the aforementioned cyclization conditions, only the β,γ-ethylenic ester **29** was isolated.



27 **28** **29**

An efficient access of a polycyclic system related to the taxane core has thus been achieved. New synthetic developments of this methodology are currently under investigation in our laboratory.

NOTES AND REFERENCES

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10 Bromomethylsafrole **22** was prepared with a 86% yield by refluxing 2 h a solution of NaBr in acetone with chloromethylsafrole (Lurik, B. B.; Volkov, Y. P. *Zh. Org. Khim.*, **1986**, *22*, 384-387).

11 **24**: oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.93 (dt, J = 15.2 Hz, J = 6.1 Hz, 1H) 6.50 (s, 1H) 6.45 (s, 1H) 5.86(s, 2H) 5.58(dt, J = 15.2 Hz, J = 3.0 Hz, 1H) 3.67 (s, 3H) 3.64 (s, 3H) 3.35 (dd, J = 6.1 Hz, J = 3.0 Hz, 1H) 2.75 (s, 2H) 2.5-2.2 (m, 6H) 1.7-1.6 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.4 (C), 177.5 (2 C), 147.2 (C), 146.9 (CH), 129.6 (C), 127.6 (2 C), 122.0 (CH), 110.7 (CH), 110.0 (CH), 101.1 (CH_2), 56.2 (CH_3), 52.1(CH_3), 48.4 (C), 41.7 (CH_2), 38.5 (2 CH_2), 35.4 (CH_2), 33.7 (2 CH_2).

12 **25**: solid, mp 210-212 °C (MeOH); $[\alpha]_D^{20}$ + 49.1 (c 1.7, CCl_4); MS (70 eV): 459 (M^+), 355, 296, 206, 175, 149, 105; IR ($CHCl_3$): 1729, 1660, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 6.65 (s, 1H), 6.43 (q, 1H, J = 7.1 Hz), 6.40 (s, 1H,), 5.90 (s, 2H), 4.99 (dt, 1H, J = 7.0 Hz, J = 2.0 Hz), 3.69 (s, 3H), 3.04 (dd, 1H, J = 13.5 Hz, J = 13.2 Hz), 2.95 (d, 1H, J = 14.5 Hz), 2.92 (dd, 1H, J = 17.9 Hz, J = 7.0 Hz), 2.83 (d, 1H, J = 14.6 Hz), 2.75 (ddd, 1H, J = 10.0 Hz, J = 2.0 Hz, J = 2.0 Hz), 2.66 (d, 1H, J = 17.9 Hz), 2.44 (d, 1H, J = 13.5 Hz), 2.30 (ddd, 1H, J = 16.5 Hz, J = 2.0 Hz J = 2.0 Hz), 2.15 (ddd, 1H, J = 16.5 Hz, J= 7.0 Hz, J = 3.0 Hz), 2.04 (dd, 1H, J = 14.1 Hz, J = 10.0 Hz), 2,00 (dd, 1H, J = 13.2 Hz, J = 7.0 Hz), 1.71 (d, 3H, J = 7.1 Hz), 1.50 (dd, 1H, J = 14.9 Hz, J = 3.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.0 (C), 168.5 (C), 146.7 (2 C), 141.8 (C), 134.2 (C), 133.4 (C), 129.9 (C), 128.7 (2 CH), 126.5 (CH), 125.4 (2 CH), 110.0 (CH), 109.7 (CH), 107.7 (CH), 100.9 (CH_2), 52.1 (CH_3), 49.9 (CH), 45.7 (C), 42.8 (CH_2), 39.5 (CH), 37.8 (CH_2), 37.5 (CH_2), 36.1 (CH), 33.8 (CH_2), 30.0 (CH_2), 15,5 (CH_3).

13 **26**: amorphous solid; $[\alpha]_D^{20}$ + 54.0 (c 3.6, CCl_4); MS (70 eV): 459 (M^+), 355, 296, 206, 175, 149, 105; IR ($CHCl_3$): 1729, 1660, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 6.65 (s, 1H), 6.42 (s, 1H), 6.10 (q, 1H, J = 7.0 Hz), 5.90 (s, 2H), 5.04 (ddd, 1H, J = 5.0 Hz, J = 2.5 Hz, J = 2.0 Hz), 3.68 (s, 3H), 3.16 (d, 1H, J = 14.0 Hz), 3.00 (dd, 1H, J = 17.0 Hz, J = 7.0 Hz), 2.97 (d, 1H, J = 14.0 Hz), 2.94 (dd, 1H, J = 14.0 Hz, J = 6.0 Hz), 2.74 (dd, 1H, J = 2.5 Hz, J = 2.0 Hz), 2.61 (d, 1H, J = 17.0 Hz), 2.38 (d, 1H, J = 14.0 Hz), 2.24 (ddd, 1H, J = 17.0 Hz, J = 5.0 Hz, J = 3.0 Hz), 2.12 (ddd, 1H, J = 17.0 Hz, J = 2.5 Hz, J = 2.5 Hz), 2.02-1.95 (m, 2H), 1.82 (d, 3H, J = 7.0 Hz), 1.50 (dd, 1H, J = 15.0 Hz, J = 3.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.5 (C), 167.6 (C), 146.0 (2 C), 141.0 (C), 134.2 (C), 133.8 (C), 128.8 (C), 128.2 (2 CH), 126.2 (CH), 125.7 (2 CH), 109.8 (CH), 109.3 (CH), 106.7 (CH), 100.0 (CH_2), 51.8 (CH_3), 51.7 (CH), 45.0 (C), 42.7 (CH_2), 39.1 (CH), 37.4 (CH_2), 36.9 (CH_2), 36.0 (CH), 33.6 (CH_2), 29.7 (CH_2), 17.2 (CH_3).

14 Analytical HPLC: Hichrom column (Spherisorb S 5 W), lenght: 25 cm, internal diameter: 4.9 mm; detection: UV at 254 nm; eluent: cyclohexane/AcOEt 90:10 ; flow rate: 2 ml min^{-1}; retention times: **25**: 7.79 min, **26**: 6.83 min.

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