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New Approaches to *Corynanthe* Alkaloids Involving the Conjugate Addition of Dialkyl Malonates to Unsaturated Thiolactams:Synthesis of (±)-3-*epi*-Dihydrocorynantheol

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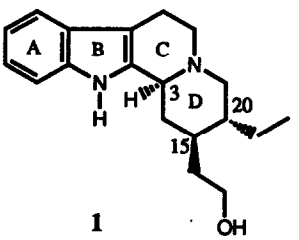
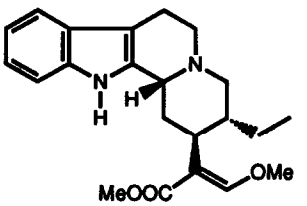
***Key words:** Michael addition; unsaturated thiolactams; Corynanthe alkaloids; (±)-3-epi-dihydrocorynantheol.*

***Abstract:** Addition of dimethyl malonate to thiolactam 8 led to a mixture of Michael adducts 9 and 10 (6:1, respectively). Compound 9 has been converted in 4 steps into (±)-3-epi-dihydrocorynantheol 16.*

Dihydrocorynantheol (corynan-17-ol) **1**[1] and hirsutine **2**[2] are two representative *Corynanthe* alkaloids. The synthesis of such tetracyclic indole alkaloids constitutes an interesting challenge, considering the presence of the three stereogenic centers at C-3, C-15 and C-20.



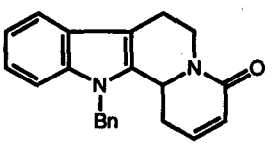
1



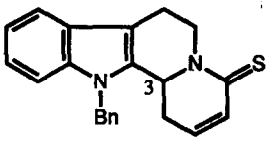
2

Numerous approaches to *Corynanthe* alkaloids have been described.[3] In the present paper, we wish to report a new general strategy for the construction of these molecules based on the conjugate addition of dialkyl malonates to tetracyclic unsaturated thiolactams, illustrated by the synthesis of (±)-3-*epi*-dihydrocorynantheol **16**.

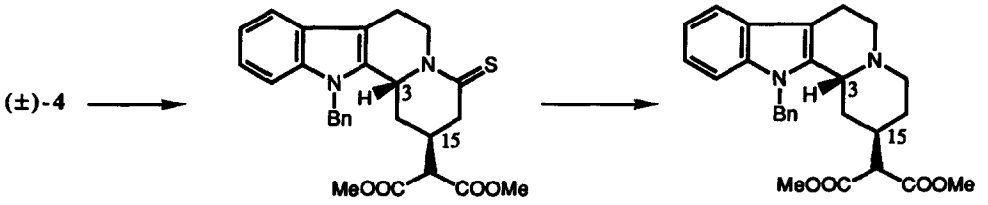
Preliminary experiments having established that the unsaturated lactam **3**[4] is unreactive towards dialkyl malonates, we decided to test the thiolactam analog **4**.[5] As expected,[7] the latter proved to be much more reactive than the parent lactam : addition of dimethyl malonate proceeded smoothly (10 eq of dimethyl malonate, 10 eq of Cs_2CO_3,[8] THF, 5h, 20°C), leading quantitatively to adduct **5**[9] ***as a single diastereomer***. This was desulfurized, according to the procedure of Raucher[10] (*i* : $Me_3O^+ BF_4^-$, *ii* : $NaBH_4$ / MeOH), into **6** (80% yield).



(±)-3



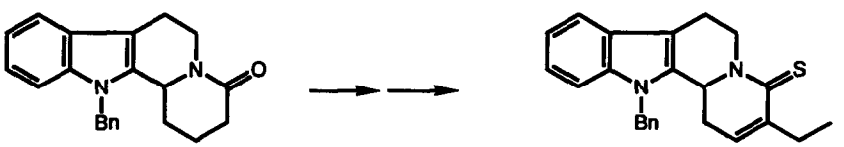
(±)-4



(±)-5 (±)-6

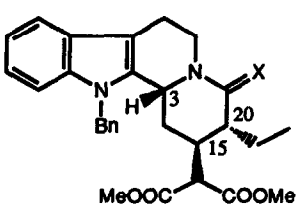
It is worthy of note that the *trans* relationship between H-3 and H-15 is observed in adduct **5**, thus reflecting, as expected,[4] the *syn* addition of dimethyl malonate relative to H-3 of thiolactam **4**.

The starting thiolactam **8**, which possesses the requisite C-20 ethyl appendage of target *Corynanthe* alkaloids, was prepared from the known tetracyclic lactam **7**[4] (*i* : LDA then EtI, *ii* : LDA then PhSeCl, *iii* : $NaIO_4$, *iv* : Lawesson's reagent, 3h, 90°C, 65% overall yield).

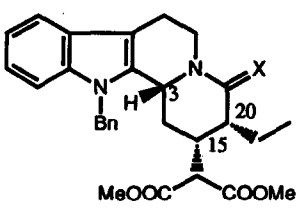


(±)-7 (±)-8

Compared to the preceding conversion [**4**→**5**], somewhat more drastic operating conditions were required to add dimethyl malonate to thiolactam **8**[11](10 eq of dimethyl malonate, 2 eq of NaOMe, MeOH/THF, 4 days at 20°C) giving an inseparable mixture of adducts **9** and **10** in the ratio 6:1 (90% yield).



(±)-**9** : X=S
(±)-**11**: X=H_2

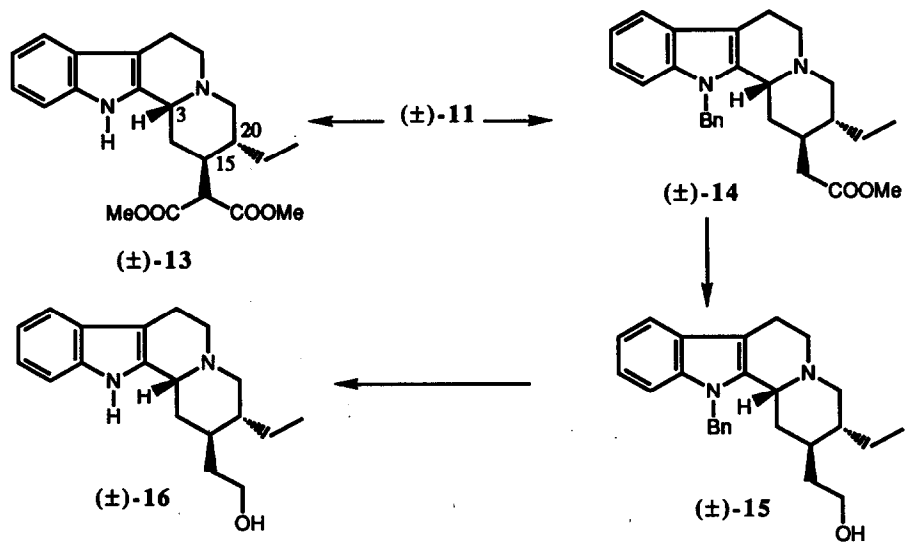


(±)-**10** : X=S
(±)-**12** : X=H_2

Upon desulfurization (Me_3O^+ BF_4^-, then $NaBH_4$, 80%),[10] **9** and **10** furnished a mixture (6:1) of compounds **11**[12] and **12**,[13] easily separated by flash chromatography on silica gel.

These stereochemical findings deserve some comments. The relationship between H-3 and H-15 is *trans* in the major Michael adduct **9** and *cis* in the minor epimer **10**. In both diastereomers, the relationship between H-3 and H-20 is *cis*. Thus, compared to the closely related reaction [**4**→**5**], the addition of dimethyl malonate to thiolactam **8** is less stereoselective.

The synthesis was pursued, by debenzylation of the major isomer **11**. Although all attempts at hydrogenolytic cleavage of the N-benzyl group of **11** were fruitless, treatment by NaH in THF, followed by sodium in ammonia, gave with a modest yield (35-40%) the expected debenzylated compound (±)-**13**, a known intermediate in the synthesis of hirsutine **2**.[2] Debenzylation of **11** furnishing a poor yield of **13** (a drawback attributed to the competitive further reduction of the ester groups of **11**), we decided to postpone this deprotection step at the final stage of our synthesis. With this aim in view, compound **11** was demethoxycarbonylated to the monoester **14** by heating with LiI in moist DMSO[14] (30 min. at 180°C, 70%). Reduction of the ester function of **14** (10 eq. of LAH, THF, 20°C) led to alcohol **15** (85% yield) which, upon debenzylation (Na/NH_3), furnished quantitatively our target, (±)-3-*epi*-dihydrocorynantheol **16**.[15]



Synthesis of (±)-**16** was thus achieved in 9 steps(25% overall yield) from the readily available tetracyclic lactam (±) **7** (11 steps, 17% overall yield from tryptamine). Since lactam **7** has been efficiently prepared in both antipodal forms,[16] this new strategy constitutes formally an expeditious route to enantiomerically pure *Corynanthe* alkaloids.

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5. **4** has been prepared in two steps with an overall yield of 60% from **7**[4](*i*: Lawesson's reagent, *ii*: *p*-toluenesulfinyl chloride/iPr_2NEt[6]). **4**: mp 70°C (AcOEt).
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9. **5**: amorphous solid; IR ($CDCl_3$,cm^{-1}) 1750, 1732; ^1H NMR (250MHz, $CDCl_3$) δ 1.78-1.97(m, 1H) 2.30(ddd, J=14.4 4.0 4.0 Hz, 1H) 2.56-2.73(m, 1H) 2.80-3.10(m, 3H) 3.18(dd, J=12.0 3.0 Hz, 1H) 3.32(dd, J=15.3 5.3 Hz, 1H) 3.40(d, J=5.8 Hz, 1H) 3.64(s, 3H) 3.70(s, 3H) 4.98(dd, J=11.0 4.0 Hz, 1H) 5.32(d, J=17.8 Hz, 1H) 5.48(d, J=17.8 Hz, 1H) 5.85(ddd, J=13.0 4.0 2.5 Hz, 1H) 6.87-7.04(m, 2H) 7.10-7.34(m, 6H) 7.52-7.66(m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$), δ 20.2(CH_2) 29.8(CH) 34.2(CH_2) 45.9(CH_2) 46.8(CH_2) 48.1(CH_2) 52.5(CH_3) 52.6(CH_3) 53.6(CH) 54.5(CH) 109.8(C) 109.9(C) 118.4(CH) 120.0(CH) 122.4(CH) 125 7(2CH) 126.0(C) 127.4(CH) 128.7(2CH) 132.9(C) 137.4(C) 138.0(C) 168.0(C) 168.5(C) 200.9(C).The H-3/H-15 *trans* relationship has been established by ^{13}C NMR analysis.[14]
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12. **11**: amorphous solid; MS(EI, 70eV) m/e 474($M^{+\cdot}$, 100) 473(89) 383(39) 343(59) 315(34) 260(23); IR ($CDCl_3$,cm^{-1}) 2821, 2768, 1756, 1733; ^1H NMR (200MHz, $CDCl_3$) δ 0.85(t, J=7.4Hz, 3H) 1.13-1.30(m, 1H) 1.40-1.73(m, 3H) 1.89(ddd, J=17.7 11.8 4.7 Hz, 1H) 2.32(br d, 1H) 2.54-3.02(m, 6H) 3.35(s, 3H) 3.65(s, 3H) 3.54-3.70(m, 1H) 3.78(d, J=11 Hz, 1H) 5.12(d, J=17.8 Hz, 1H) 5.28(d, J=17.8 Hz, 1H) 6.84-7.06(m, 5H) 7.09-7.25(m, 3H) 7.37-7.49(m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 12.1(CH_3) 22.0(CH_2) 25.9(CH_2) 29.4(CH_2) 37.1(CH) 38.6(CH) 47.6(CH_2) 52.3(2 CH_3 and CH_2) 54.0(CH) 54.3(CH_2) 55.0(CH) 109.7(CH) 109.8(C) 117.9(CH) 119.3(CH) 121.3(CH) 125.8(2CH) 127.0(CH) 127.1(C) 128.5(2CH) 136.2(C) 137.9(C) 138.0(C) 168.9(2C).
13. **12**: amorphous solid; MS(EI, 70eV) m/e 474($M^{+\cdot}$, 100) 473(88) 383(26) 344(24) 343(84) 315(29) 274(46) 260(33); IR ($CDCl_3$,cm^{-1}) 2830, 2780, 1750, 1730; ^1H NMR (200MHz, $CDCl_3$) δ 0.82(t, J=7.2 Hz, 3H) 1.15-1.48(m, 2H) 1.52-1.81(m, 3H) 2.33-2.72(m, 4H) 2.75-3.05(m, 3H) 3.20(d, J=10Hz, 1H) 3.22(s, 3H) 3.35(br d, J=10.0 Hz, 1H)3.63(s, 3H) 5.10(d, J=17.6, 1H) 5.24(d, J=17.6, 1H) 6.89-7.09(m, 5H) 7.09-7.15(m, 3H) 7.35-7.46(m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 12.5(CH_3) 18.3(CH_2) 22.6(CH_2) 30.9(CH_2) 37.7(CH) 41.2(CH) 48.0(CH_2) 52.1(CH_3) 52.3(CH_2) 52.4(CH_3) 54.5(CH) 57.7(CH_2) 60.2(CH) 109.6(CH) 118.1(CH) 119.4(CH) 121.4(CH) 125.9(2CH) 127.0(CH) 128.6(2CH) 136.2(C) 137.6(C) 138.0(C) 168.4(C) 168.8(C).
The C-3/C-15 and C-15/C-20 stereochemical relationships in compounds **11** and **12** have been determined by NOE difference experiments.
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15. **16**: solid, mp 85°C (cyclohexane); HRMS (EI, 70 eV) calcd. for $C_{16}H_{26}N_2O$: 298.2045, found : 298.2045; MS(EI, 70eV) m/e 298($M^{+\cdot}$, 87) 297(100) 253(20) 225(30) 170(32) 169(30) 156(24); IR (KBr, cm^{-1}) 3265, 2805, 2764; ^1H NMR (200MHz, $CDCl_3$) δ 0.76(t, J=7.0 Hz, 3H) 1.02-1.90(m, 7H) 1.96-2.20(m, 1H) 2.34-3.20(m, 7H) 3.67(m, 2H) 3.90(br s, 1H) 6.92-7.12(m, 2H) 7.13-7.30(m, 1H) 7.39(m, 1H) 8.19(br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$), δ 11.7(CH_3) 18.7(CH_2) 24.3(CH_2) 31.7(CH_2) 32.6(CH) 35.3(CH_2) 41.6(CH) 51.7(CH_2) 52.1(CH_2) 54.4(CH) 60.4(CH_2) 107.5(C) 110.9(CH) 117.9(CH) 119.1(CH) 121.0(CH) 127.5(C) 133.9(C) 135.9(C). *Lit* : mp 84-87°C (Ziegler, F.E.; Sweeny, J.G. *Tetrahedron Lett.*, **1969**, 1097-1100).
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