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EFFECT OF A-STRAIN. DIASTEREOSELECTIVE SYNTHESIS OF 3,2'-METHYLENE BRIDGED CIS-4a-ARYLDECAHYDROISOQUINOLINE RING SYSTEM VIA N-ACYLIMINIUM ION-POLYENE RING CLOSURE

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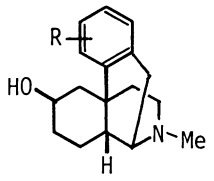
Diastereoselective synthesis of 3,2'-methylene bridged 6-oxygenated 4a,6-cis-4a,8a-cis-4a-aryldecahydroisoquinoline ring system was achieved by an application of N-acyliminium ion-polyene cyclization at the initial stage.

Biomimetic polyene cyclizations have been applied to the synthesis of multicyclic compounds with excellent stereocontrol.[1,2] Polyene cyclizations by using N-acyliminium ion as a cationic initiating center[3] have also been applied to a synthesis of N-polycyclic compounds in a stereocontrolled manner.[4] As a part of our general investigations on the N-acyliminium ion-polyene cyclizations,[5] we investigated a synthesis of a new tetracyclic isoquinoline ring (2), a positional isomer of isomorphinan ring system (1) with regard to benzyl methylene bridge, by an application of an N-acyliminium ion-polyene cyclization at the initial stage. The results of our studies are herein described.



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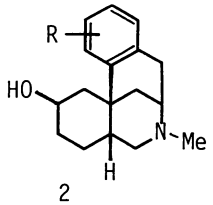

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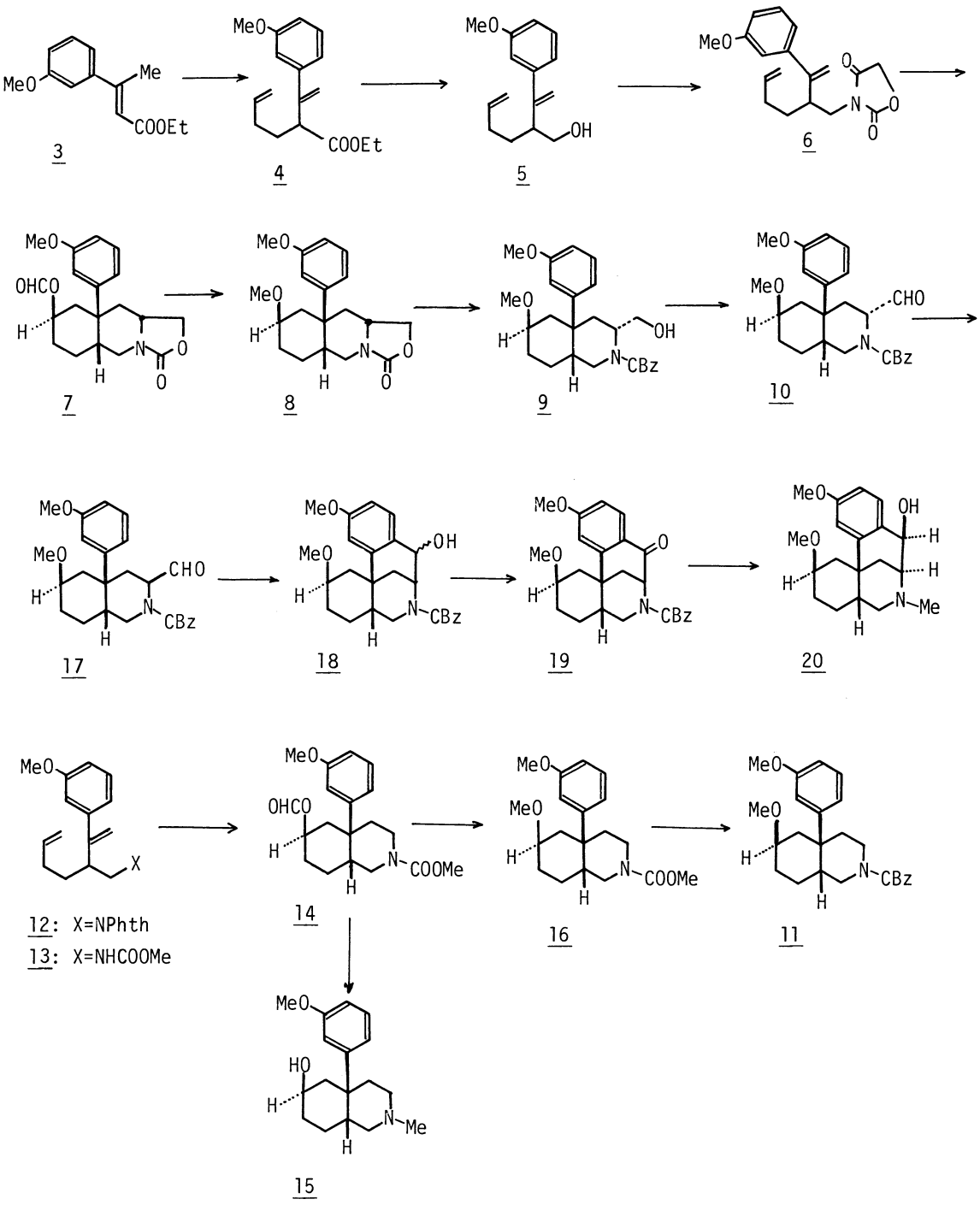
α-Butenylation of the ester (3) (LDA, 1-iodo-3-butene, THF, -78 °C ⟶ 20 °C) gave the ester (4),[6] bp 155 °C (2 Torr), in 80% yield, reduction of which ($LiAlH_4$, Et_2O, 0 °C, 2 h) yielded the alcohol (5) as an oil in 82.5% yield. Condensation of 5 with oxazolidine-2,4-dione by Mitsunobu's method[7] gave 6 as an oil in 92% yield. Reduction of 6 (DIBAH, Et_2O, -78 °C), followed by cyclization with formic acid gave the tricyclic isoquinoline (7),[6] mp 149-151 °C, in 68% yield as a single diastereomer. Hydrolysis of 7 (3M NaOH-MeOH, room temperature, 1 h), followed by methylation (NaH, DMF, CH_3I) afforded 8,[6] mp 136-138 °C, in 62% yield. Hydrolysis of 8 (15 equiv. KOH-EtOH, reflux), followed by benzyloxycarbonylation with benzyl chloroformate afforded 9 as an oil in 94% yield. Swern oxidation[8] of 9 (Me_2SO, Et_3N, oxalyl chloride) gave 10[6] as an oil in 94% yield. In order to confirm the ring-juncture and the relative configuration at the 6-position of 10, decarbonylation of 10 with $(Ph_3P)_3RhCl$[9] was carried out to give 11, as an oil, in 52% yield, which was identified with the authentic specimen


MeO
Me
COOEt
3
MeO
COOEt
4
MeO
OH
5
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O
N
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O
6
MeO
OHCO
H
N
O
H
O
7
MeO
MeO
H
N
O
H
O
8
MeO
MeO
H
OH
N
CBz
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9
MeO
MeO
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CHO
N
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10
MeO
MeO
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CHO
N
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MeO
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18
MeO
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CBz
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19
MeO
OH
MeO
H
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Me
H
20
MeO
X
12: X=NPhth
13: X=NHCOOMe
MeO
OHCO
H
N
COOMe
H
14
MeO
MeO
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N
COOMe
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16
MeO
MeO
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MeO
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15

alternatively prepared as follows.

Condensation of 5 with phthalimide by Mitsunobu's method[7] gave 12. Decomposition of 12 with hydrazine hydrate, followed by methoxycarbonylation with methyl chloroformate yielded 13 as an oil in 67% yield. Cyclization of 13 with paraformaldehyde in formic acid gave 14[6] as an oil in 62% yield as a single diastereomer. Reduction of 14 ($LiAlH_4$, THF, 25 °C, 12 h) gave 15, mp 95-97 °C (lit.[10] 95-97 °C), in 83% yield, the spectral data of which were identical with those of the authentic specimen[10] in all respects and not identical with those of the other three diastereomers. The four diastereomers can be easily distinguished by comparison with their physical data.[10] Thus, the stereochemistry of 14 was clearly established as 4a,6-cis-4a,8a-cis. Then 14 was converted to 11 through the usual way via 16. This high diastereoselective cis-ring closure can be accounted for by the significant A-type strain in the monocyclized cationic intermediate.[5,11] Furthermore, the relative configuration at the 3-position of 10 was deduced as 3,4a-trans by the facts that any attempt to cyclize 10 was not successful, although the cyclization smoothly occurred in the case of the epimerized 3-formylisoquinoline (17).

Epimerization at the 3-position in 10 was carried out by treatment with t-BuOK (1 equiv., Et_2O, -5 °C) to give 17[6] as an oil in 72% yield. Apparently, epimerization proceeded through enolation and concomitant protonation procedure. The epimerization at the 3-position is not surprizing in line with the A-strain ideas.[11,12] and it is known that an A-strain can pit agaist 1,3-interaction.[11] Two sets of characteristic signals were observed in the ^1H NMR spectrum of 17. This might be caused by inhibition of free rotation of phenyl and formyl group owing to 1,3-interaction. Cyclization of 17 ($BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C, 1 min), followed by oxidation of 18 with Jones reagent gave 19[6] as an oil in 60% yield. Aromatic proton signals in its ^1H NMR spectrum indicated that cyclization occurred at the para-position of OCH_3 group. On reduction of 19 with $LiAlH_4$, hydride attacked from the less hindered side to give 20,[6] mp 159-162 °C, in 98% yield, with high diastereoselectivity.

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6) All new compounds gave satisfactory microanalyses, IR, ^{1}H NMR (90 MHz), and Mass spectral data. Selected spectral data are as follows. Only characteristic signals were given for ^{1}H NMR spectra.

7: m/e 345 (M^+), IR ($CHCl_3$) 1750, 1725 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.20 (1H, dd, J=3 and 15 Hz), 3.52 (1H, broad d, J=15 Hz), 3.57-4.03 (1H, m), 3.90 (1H, dd, J=6 and 8 Hz), 4.30 (1H, dd, J=8 and 8 Hz), 5.07 (1H, m, $W_{1/2}$= 28 Hz), 6.80 (1H, dd, J=2 and 8 Hz), 6.91 (1H, d, J=2 Hz), 6.97 (1H, d, J=8 Hz), 7.30 (1H, dd, J=8 and 8 Hz), 7.92 (1H, s).

8: m/e 331 (M^+), IR ($CHCl_3$) 1750 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.21 (1H, dd, J=4 and 15 Hz), 3.30 (3H, s), 3.53 (1H, broad d, J=15 Hz), 3.82 (3H, s), 3.97 (1H, dd, J=6 and 8 Hz), 4.37 (1H, dd, J=8 and 8 Hz), 6.87 (1H, dd, J=2 and 8 Hz), 6.99 (1H, d, J=2 Hz), 7.03 (1H, d, J=8 Hz), 7.39 (1H, dd, J=8 and 8 Hz), ^{13}C NMR ($CDCl_3$) δ 25.4 (t), 31.5 (t), 33.0 (t), 36.96 (d), 41.9 (s), 42.7 (t), 48.1 (t), 51.0 (d), 55.17 (q), 56.64 (q), 67.6 (t), 75.12 (d), 110.5 (d), 112.8 (d), 117.8 (d), 130.0 (d), 146.7 (s), 157.5 (s), 160.1 (s).

10: m/e 437 (M^+), IR ($CHCl_3$) 1730, 1690 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.20 (1H, dd, J=3 and 15 Hz), 3.24 (3H, s), 3.20-3.51 (1H, m), 3.51-3.74 (2H, m), 3.78 (3H, s), 5.08 (2H, s), 6.78 (1H, dd, J=2 and 8 Hz), 6.91 (1H, d, J=2 Hz), 6.96 (1H, d, J=8 Hz), 7.32 (5H, s), 9.52 (1H, d, J=3 Hz).

14: m/e 347 (M^+), ^{1}H NMR ($CDCl_3$) δ 2.76 (1H, d with small spliting, J=12 Hz), 3.05 (1H, dd, J=3 and 12 Hz), 3.68 (3H, s), 3.80 (3H, s), 5.12 (1H, m, $W_{1/2}$= 30 Hz), 6.85 (1H, dd, J=2 and 8 Hz), 6.98 (1H, d, J=2 Hz), 7.02 (1H, dd, J=2 and 6 Hz), 7.35 (1H, dd, J=6 and 8 Hz), 7.98 (1H, s).

17: m/e 437 (M^+), IR ($CDCl_3$) 1740, 1690 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.28 (3H, s), 3.73 (3H, s), 4.46-4.63 (0.4H, m), 4.63-4.81 (0.6H, m), 5.07 (0.8H, s), 5.12 (1.2H, s), 6.74 (1H, dd, J=2 and 8 Hz), 6.84 (1H, d, J=2 Hz), 7.22 (1H, dd, J=8 and 8 Hz), 7.27 (2H, s), 7.33 (3H, s), 8.97 (0.4H, s), 9.00 (0.6H, s).

19: IR ($CHCl_3$) 1700 cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 2.49 (1H, dd, J=4 and 15 Hz), 2.87 (1H, d with small spliting, J=15 Hz), 3.39 (3H, s), 3.86 (3H, s), 4.92 (1H, m), 5.18 (2H, broad s), 6.87 (1H, dd, J=2 and 9 Hz), 6.99 (1H, d, J=2 Hz), 7.35 (5H, broad s), 8.08 (1H, d, J=9 Hz).

20: m/e 317 (M^+), ^{1}H NMR ($CDCl_3$) δ 2.58 (1H, dd, J=5 and 8 Hz), 2.76 (3H, s), 3.10 (1H, broad t, J=5 Hz), 3.27 (3H, s), 3.27-3.77 (2H, m), 3.76 (3H, s), 4.62 (1H, d, J=6 Hz), 6.80 (1H, dd, J=2 and 9 Hz), 6.83 (1H, d, J=2 Hz), 7.50 (1H, d, J=9 Hz).

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