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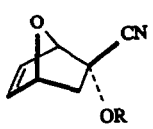
STEREOSELECTIVE AMINO-HYDROXYLATION OF THE DOUBLE BOND IN 7-OXABICYCLO[2.2.1]HEPT-5-EN-2-YL DERIVATIVES. REMOTE SUBSTITUENT PARTICIPATION IN ACID-CATALYZED DECOMPOSITIONS OF AZIRIDINES AND TRIAZOLINES

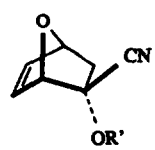
Jean-Louis Reymond and Pierre Vogel*
Institut de chimie organique de l'Université,
2, rue de la Barre, CH-1005 Lausanne, Switzerland.

Summary: *An efficient method has been developed for the stereoselective substitution of 7-oxabicyclo[2.2.1]hept-2-yl derivatives by protected amino group at C(5-exo) and hydroxy group at C(6-endo).*

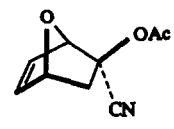
The 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivatives **1** - **6** can be obtained optically pure.[1] Because of their bicyclic structure, the double-bond at C(5)-C(6) reacts with high *exo* face selectivity.[2] The regioselectivity of electrophilic additions of these systems depends on the nature of the substituents at C(2).[2a,3] For instance, while the CN and camphanyloxy groups in **1**, or CN and OAc group in **7**, play the role of electron-withdrawing substituents, giving exclusively adducts of type **8**, the carbonyl group in **4** acts as an electron-donating substituent and leads to the formation of adducts **9**.[3] Adducts **8** can be transformed into ketones **10**, regioisomeric with **9**. Ketones **9** and **10** can be substituted stereoselectively at C(3) and then transformed into a variety of compounds, including sugar derivatives of biological interest.[4]



R = (1S)-camphanoyl **1**
R = Ac **7**



R' = (1R)-camphanoyl **2**



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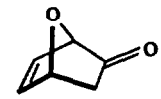

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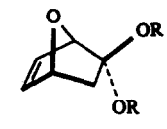
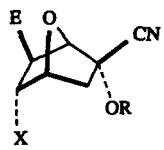


R = Me **5**
R = $PhCH_2$ **6**



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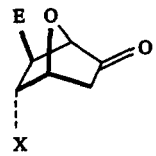
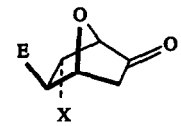
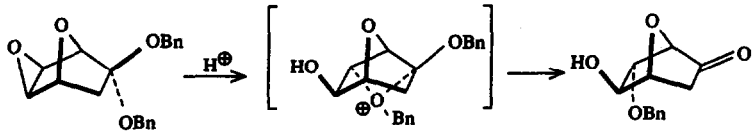




9

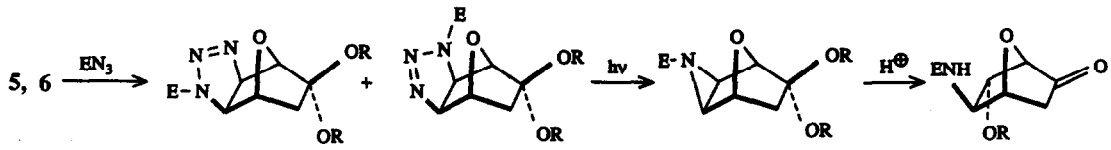
Stereospecific substitution at C(5) and C(6) can also be carried out through acid-promoted rearrangement of the epoxy-acetal **11**.[5] On treatment of **11** with HSO_3F and $PhCH_2OH/CH_2Cl_2$ the *trans* disubstituted derivative **13** was obtained in 88 % yield. The advantage of this method is that the *endo* group OH at C(6) in **13** is protected as a benzyl ether whereas the *exo* group OH at C(5) is unprotected. Reaction **11** → **13** probably involves the intermediacy of oxonium ion **12**. We report preliminary results on a similar approach that is now applied to introduce a protected amino function at C(5-*exo*) and a protected hydroxy group at C(6-*endo*) of 7-oxabicyclo[2.2.1]heptan-2-one.



11 12 13

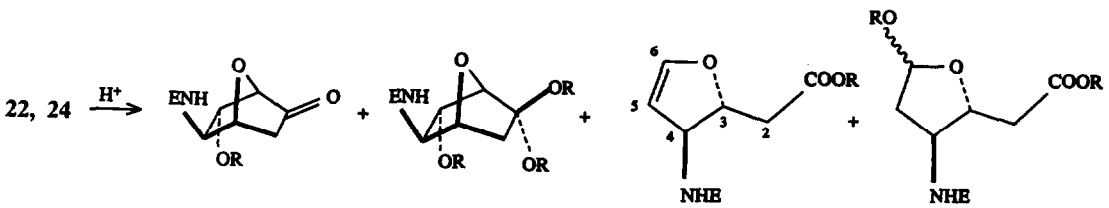
Acetals 5 and 6[5] reacted with one equivalent of ethyl azidoformate ($CHCl_3$, 55 °C, 24 h) to give 9:8 mixtures of the crystalline triazolines 14 + 15 (80 %) and 16 + 17 (80 %), respectively.[6] Irradiation (acetone, quartz, 125 W high pressure Hg lamp, 0 °C, Ar, 3 h) gave aziridines 18 and 19, respectively, nearly quantitatively.

On treatment of the crude 18 and 19 in CH_2Cl_2 with 5 equiv. of CF_3COOH (0 °C, 30 min), ketones 20 and 21, respectively, were isolated in moderate yields (20 - 40 %).[7] Similarly, 5 and 6 added to tertiobutyl azidoformate ($BOCN_3$) and afforded 1:1 mixtures of triazolines 22 + 23 and 24 + 25, respectively. Irradiation gave aziridines 26 and 27, that furnished 28 and 29 (20 - 30 %), respectively, on treatment with CF_3COOH in CH_2Cl_2. When recrystallized aziridines 26 and 27 were treated with 1.3 equiv. of CF_3COOH in $CHCl_3$ (20 °C, 24 h), ketones 28 and 29, respectively, were isolated in good yields (80 - 90 %), without loss of the BOC group.



E = COOEt,	R = Me	14	15	18	20
E = COOEt,	R = CH_2Ph	16	17	19	21
E = BOC,	R = Me	22	23	26	28
E = BOC,	R = CH_2Ph	24	25	27	29

On protonation, triazolines are known to decompose into N_2 and carbenium ion intermediates that usually lead to mixtures of products.[8] The triazoline 22 (42 %) could be separated from its isomer 23 by crystallization from $CHCl_3/Et_2O$ (20 °C). 24 (46 %) was separated from 25 (40 %) by column chromatography on silica gel. On treating 22 with $AcOH/CH_2Cl_2$ 1:10 and 0.02 equiv. of TMSOTf (-10 °C, 10 min) a mixture was obtained from which the compounds of MeO group migration 28 (34 %) and 30 (16 %) were isolated by crystallization from ether, followed by separation by chromatography on silica gel. Products 31 (20 %) and 32 (6 %), resulting from C(1)-C(2) bond leakage, were isolated, together with 1.5 % of aziridine 26, by chromatography of the mother-liquor. Under the same conditions, triazoline 24 afforded 29 (24 %), 33 (19 %), 34 (7 %) and 35 (17 %).

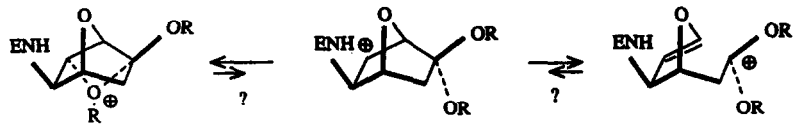


R = Me	28	31	32
R = $PhCH_2$	29	34	35

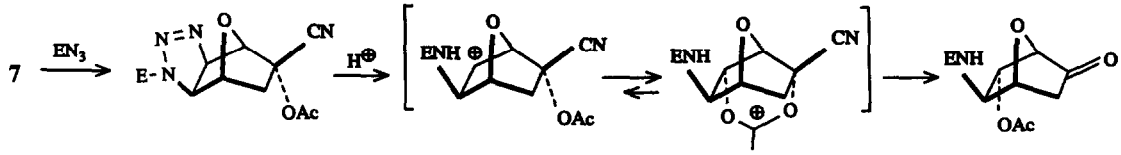
E = BOC

The stereoselective acid-promoted transformations 18 → 20, 19 → 21, 26 → 28 and 27 → 29 can be interpreted in terms of the formation of oxonium ion intermediates 36 (analogous to 12) arising from the participation of the *endo* OR group of the acetals to the heterolysis of the C(6)-N bond. The intermediacy of

7-oxabicyclo[2.2.1]hept-2-yl cations **37** might be invoked to explain the acid-promoted decompositon of triazolines **22** and **24**. Intermediates **37** are expected to undergo concurrent cyclization to **36** and bond leakage to **38**.

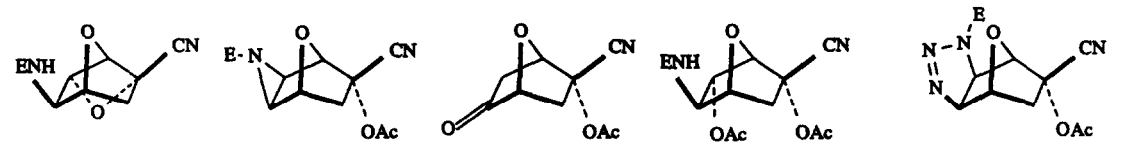


36 **37** **38**



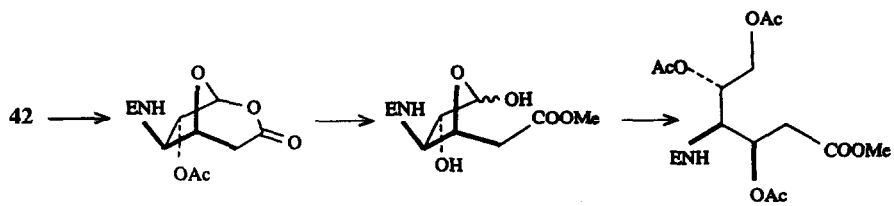
E = COOEt **39** **40** **41** **42**

A shorter synthesis of disubstituted 7-oxanorbornanones was realized by the acidic decompositon of triazoline **39** derived from **7**. It features a 1,3-migration of the *endo* acetoxy group in **39**. In 7:3 $MeOH/H_2O$ at 37 °C (7 d), ethyl azidoformate added to **7** and gave **39** (65 %, isolated). Treatment with 1:10 $AcOH/CH_2Cl_2$ and 0.16 equiv. of TMSOTf at -10 °C (1 h), followed by aqueous work-up with K_2CO_3 and formaline (to deplace the cyanohydrines, 0 °C, 50 min) afforded pure ketone **42** in 72 % yield. This result can be interpreted in terms of formation of ion **40** which is quenched intramolecularly with the *endo* acetoxy group to give the more stable ion intermediate **41**. The latter reacts with the medium to give **42**. This hypothesis is consistent also with the minor products **43** (10 %), **44** (6.7 %), **45** (2.5 %) and **46** (0.9 %) that were formed concurrently and were isolated from the mother-liquor of crystallization of **42**.



43 **44** **45** **46** E = COOEt **47**

The dipolar addition of ethyl azidoformate to **7** was not regiospecific! When run in acetone at 60 °C (48 h) a 2:1 mixture of **39** and **47** was obtained. The reaction can be catalyzed with $Zn(OAc)_2$, CuCN or $NiCl_2$ and occurs at 20 °C (without solvent, 4 d) to give a 2:1 mixture of **39** and **47**. The structures of all the new compounds presented here were confirmed by their elemental analysis and their spectral data.[7,10] The relative configuration of H-C(5) and H-C(6) of the 7-oxabicyclo[2.2.1]hept-2-yl derivatives was given by their coupling constants with the vicinal protons in their ^{1}H-NMR (360 MHz) spectra.[2a,11] In particular, the *trans* relationship for H-C(5) and H-C(6) in **20**, **21**, **28** - **30**, **33** and **42** was confirmed by ^3J(H-C(5), H-C(6)) < 1 Hz.[7]



48 **49** **50**

Compounds **20**, **21**, **28** - **30**, **33** and **42** are expected to become useful synthetic intermediates for the synthesis of natural compounds, or/and products of biological interest. Preliminary studies have shown that **42** can be oxidized selectively with metachloroperbenzoic acid ($CHCl_3$, 20 °C, 1 h) into lactone **48**. Treatment with $MeOH/Na_2CO_3$ gave **49**. Reduction of **49** with $NaBH_4$/MeOH, followed by treatment with Ac_2O/pyridine gave **50**, a potential synthetic intermediate for the preparation of 4-amino-2,4-dideoxy-*lyxo*-hexose.

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7. Characteristics of **20** : m.p. 98 - 99 °C; IR ($CHCl_3$) : 3040, 3000, 2930, 1768, 1710, 1510. ^{1}H-NMR ($CDCl_3$) : δ_H 5.47 (br.d, J = 8, NH); 4.63 (d, J = 6, H-C(4)); 4.38 (d, J = 5, H-C(1)); 4.1 (q, J = 7), 1.21 (t, J = 7, CH_3CH_2); 3.89 (d, J = 8, H-C(5)); 3.7 (d, J = 5, H-C(6)); 3.36 (s, MeO); 2.46 (dd, J = 18, 6, Hexo-C(3)); 2.19 (d, J = 18, Hendo-C(3)); **22** : m.p. 155 - 158 °C (dec.); IR ($CHCl_3$) : 3000, 1975, 1735, 1700; ^{1}H-NMR ($CDCl_3$) : 5.19 (d, J = 8.5, H-C(6)); 4.72 (s, H-C(1)); 4.69 (d, J = 6, H-C(4)); 3.99 (d, J = 8.5, H-C(5)); 3.29, 3.25 (2s, 2 MeO); 2.03 (dd, J = 13, 6, Hexo-C(3)); 1.64 (d, J = 13, Hendo-C(3)); 1.57 (s, BOC); **24** : m.p. 126 - 127 °C; **25** : m.p. 125 - 127 °C; **26** : m.p. 87 - 87.5 °C; IR ($CHCl_3$) : 3000, 2970, 2930, 1707, 1365, 1328; ^{1}H-NMR ($CDCl_3$) : 4.57 (d, J = 5.5, H-C(4)); 4.43 (s, H-C(1)); 3.27 (s, 2 MeO); 2.87 (d, J = 3.5, H-C(6)); 2.73 (d, J = 3.5, H-C(5)); 2.08 (dd), 1.68 (d, $H_2C(3)$); 1.45 (s, BOC); **27** : m.p. 118.5 - 119.5 °C; **28** : m.p. 101 - 101.5 °C; **29** : m.p. 123 - 123.5 °C; IR ($CHCl_3$) : 3430, 3000, 1768, 1702, 1500; **30** : m.p. 93 - 94 °C; **31** : m.p. 56.5 - 57 °C; ^{1}H-NMR ($CDCl_3$) : 6.46 (dd, J = 3, 1.5, H-C(6)); 4.96 (dd, J = 3, 3, H-C(5)); 4.69 (ddd, J = 9.5, 3.5, 3.5, H-C(3)); 4.68 (br.s, NH); 4.57 (m, H-C(4)); 3.74 (s, MeOH); 2.76 (br.dd, J = 16.5, 3.5), 2.65 (br.dd, J = 16.5, 9.5, $H_2C(2)$); 1.46 (s, BOC); **32** : m.p. 72 - 78 °C; **33** : m.p. 137 - 138.5 °C; **34** : m.p. 71.5 - 72 °C; **42** : m.p. 102 - 103 °C; IR ($CHCl_3$) ; 3445, 3030, 1774, 1742, 1720. ^{1}H-NMR ($CDCl_3$) : 5.26 (br.d, J = 8, NH); 4.85 (d, J = 5.5, H-C(1)); 4.74 (d, J = 6.5, H-C(4)); 4.56 (d, J = 5.5, H-C(6)); 4.15 (q), 1.26 (t, CH_3CH_2); 4.06 (br.d, J = 8, H-C(5)); 2.58 (dd, J = 18.0, 6.5), 2.26 (d, J = 18, $H_2C(3)$); 2.06 (s, Ac); **43** : m.p. 94 - 97 °C; **44** : m.p. 86 - 87 °C; **45** : m.p. 145 - 150 °C (dec.); **46** : 139 - 144 °C; **47** : 140 - 142 °C (dec.); **48** : m.p. 84 - 85 °C; ^{1}H-NMR ($CDCl_3$) : 5.98 (d, J = 4, H-C(1)); 5.22 (br.d, J = 6, NH); 4.91 (dd, J = 4, 3.5, H-C(7)); 4.56 (d, J = 6.5, H-C(5)); 4.14 (q); 1.26 (t, CH_2CH_3); 4.08 (dm, J = 6, H-C(6)); 3.10 (dd, J = 18.5, 6.5); 2.76 (br.d, J = 18.5, $H_2C(4)$); 2.14 (s, Ac).
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9. Acid promoted decompositions of **23** and **25** gave mixtures of products arising from Wagner-Meerwein rearrangements of the corresponding 7-oxabicyclo[2.2.1]hept-2-yl cation intermediates.[10]
10. Details will be given in our full-paper.
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