Strategy for a Seven-Membered Ring Closure with Bicyclic Framework

Jean-Marc Duffault
Unité de Phytopharmacie et Médiateurs Chimiques, I.N.R.A., Route de Saint-Cyr, F-78026 Versailles Cedex, France
Fax : 33 1 30 83 31 49 ; E-mail : duffault@versailles.inra.fr
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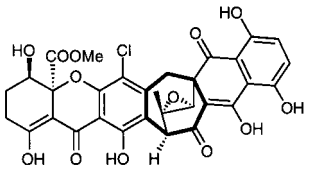
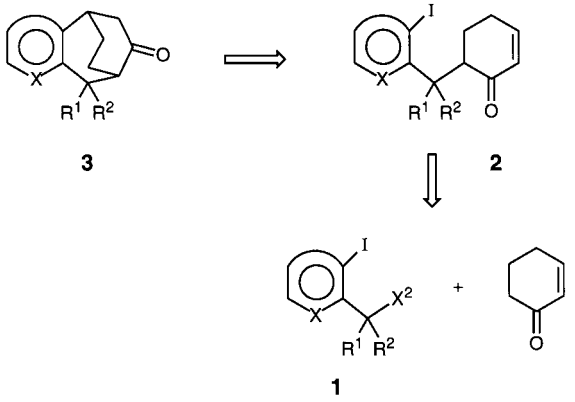
Abstract : Radical-induced cyclisations to form 7-membered rings with bicyclic framework were achieved by tributyltin hydride (TBTH) and α, α'-azobis(isobutyronitrile) (AIBN).

Our investigations to develop new synthetic methodologies in order to identify the active pharmacophore of Beticolin[1] and Cebetin[2] have allowed to favour the 7-*endo-trig* ring closure[3].



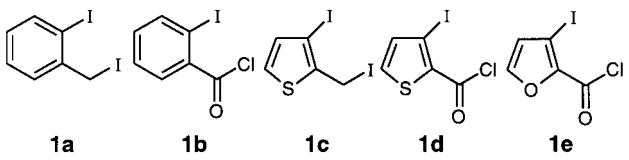
Beticolin 2

In this paper, we describe the application of synthetically useful radical-mediated cyclisations[4]. Tri-n-butyltin hydride promoted intramolecular addition[5] of the aryl iodide to an enone in **2** was expected to provide the bicyclic framework **3**. Our retrosynthetic planning was to achieve the coupling of compound **1** with 2-cyclohexen-1-one to give **2**. This intermediate **2** would then be converted into [3.2.2]-bicyclic ring **3** (Scheme 1).



Scheme 1

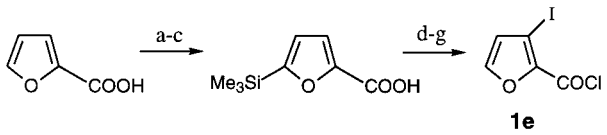
In order to be in the best conditions, we have chosen to use iodide for the transferability of tin radicals and aryl group for the reactivity of R· toward tin hydride. In this approach, we have varied the nature of the aromatic (phenyl, thienyl, furanyl) and also the electrophilic group ($CR^1R^2X^2$=CH_2I or COCl) (Scheme 2).



Scheme 2

The reaction of 2-iodobenzyl alcohol with tosyl chloride and NaI afforded product **1a**. Compound **1b** was obtained from 2-iodobenzoic acid by usual methods[6]. Compound **1d** was prepared by treatment of thiophene-2-carboxylic acid with 2.2 equivalents of n-BuLi in THF at -78°C to yield the intermediate ortho dilithioarylcarboxylic acid which provided the 3-iodothiophene-2-carboxylic acid by subsequent addition of iodine as electrophile[7]. This acid was converted into its acid chloride with oxalyl chloride. Compound **1d** reacted with methanol to give the corresponding ester which was selectively reduced[8] to the required alcohol with DIBAL-H in toluene at -78°C. This alcohol was treated with tosyl chloride and NaI (similar to **1a**) to led to the diiodide **1c**.

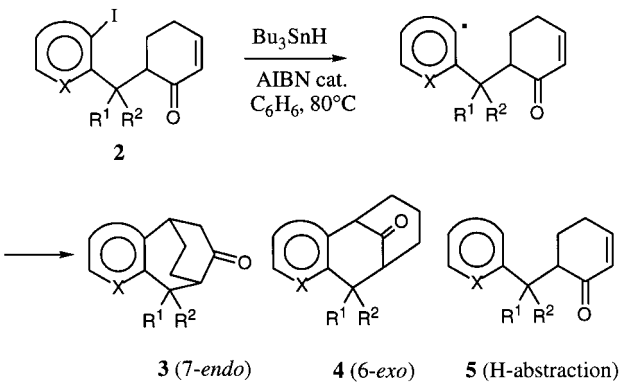
The low regioselectivity of metallation of furan carboxylic acid led us to protect the 5-position with a trimethylsilyl group. Metallation[9] followed by iodination, desilylation and conversion into the acid chloride gave **1e** in 79 % yield (Scheme 3).



Scheme 3. Reagents : a) LDA, THF, -78°C, 0.5 h ; b) TMSCl, -78°C to -25°C ; c) HCl aq, r.t .; d) n-BuLi, THF, -78°C, 0.5 h ; e) I_2, -78°C, 5h ; f) n-Bu_4NF, THF, reflux, 12 h ; g) $(COCl)_2$, CH_2Cl_2, r.t., 2 h

Selective enolisation[10] of 2-cyclohexen-1-one with 1.5 equiv. of lithium bis(trimethylsilyl)amide (LiHMDS) in THF at -78°C and reaction of the formed silyl enol ether with precursors **1** in THF-HMPA provided compounds **2** in 24-67% yields. The medium yields are due to the utilisation of the acids chloride crude and to the instability of the diiodo compounds.

Having all the necessary starting material, the final reaction was performed by a free radical halogen abstraction followed by intramolecular coupling[11] to give **3** as major product[12] (Scheme 4).
The results[13] of the cyclisation of **2** are shown in Table 1.



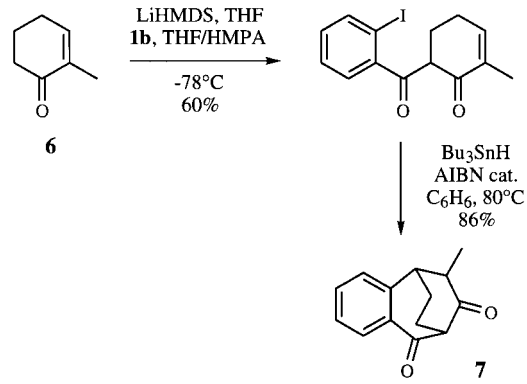
Scheme 4

Table 1. Cyclisation of **2**

Product **2**	CR^1R^2	X	Yield[a] (%)	Ratio[b] **3**	**4**	**5**
2a	CH_2	CH	98	93	7	0
2b	CO	CH	77	78	12	10
2c	CH_2	S	81	90	10	0
2d	CO	S	72	73	27	0
2e	CO	O	56	65	25	10

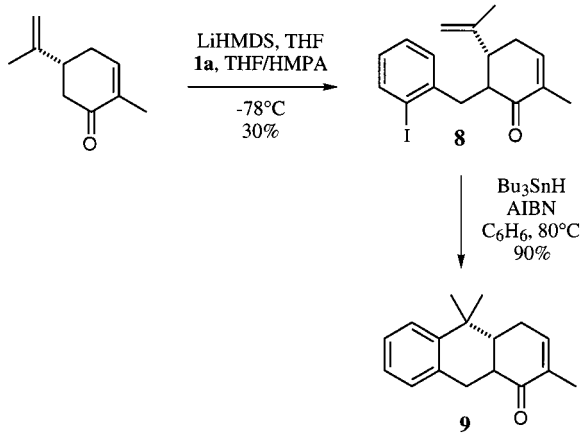
[a] Yield for the mixture (**3**+**4**+**5**)
[b] Ratio determined by gas chromatography

The compound **6**[14] substituted at the α-alkene center with methyl group gave only the product **7** by intramolecular addition to the double bond (Scheme 5).



Scheme 5

The coupling of (*R*)-(-)-carvone with **1a** led to the precursor **8** in 30% yield. The radical cyclisation afforded only product **9** (Scheme 6).



Scheme 6

In the first case, the radical has been closed only by the 7-*endo-trig* process, it should be helpful for the subsequent introduction at this position of the keto group necessary for beticolin synthesis. The second case gave the 6-*exo-trig* mode (thermodynamically more stable product), indeed the presence of double bonds has made the system more complex.

In summary, we have succeeded in the synthesis of seven-membered ring radical-mediated cyclisations. These results should be useful for designing beticolin 2 and cycloheptanyl analogs. Related studies are in progress and will be reported later.

Acknowledgment. We are indebted to Jacqueline MAHUTEAU (Faculté de Pharmacie, Chatenay-Malabry) and Claude MERIENNE (Université Paris XI, Orsay) for NMR experiments and their interpretation.

References and Notes

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(13) Typical experimental procedure : To a stirred and refluxing solution of **2** (2 mmol) containing azoisobutyronitrile (AIBN) (0.2 equiv.) in dry benzene (6 ml), tributyltin hydride (2 equiv.) was added dropwise over 2 h. The reaction mixture was continued at this temperature for 4 h, then cooled to 0°C and quenched with H_2O (10 ml). The residue was extracted with dichloromethane, washed with H_2SO_4 (1N), $NaHCO_3$ sat. and NaCl sat. solutions. The organic phase was dried over $MgSO_4$, filtered and evaporated under vacuum. The residue was subsequently purified by flash column chromatography on silica gel with CH_2Cl_2 as eluent and HPLC using a Nucleosil 5 C_{18} column eluted with CH_3CN/TFA (1%) to give **3** and **4**.
Selected data : e.g. **3d** ; ^{13}C NMR (75.5 MHz, $CDCl_3$) : 207.54 (CO), 190.22 (CO), 136.27 (C quat.), 129.25 (C quat.), 128.44 (CH), 126.47 (CH), 50.67 (CH), 33.13 (CH_2), 25.64 (CH_2), 24.51 (CH_2), 17.27 (CH). MS : m/z (EI) : 206 ($M^{+\cdot}$, 100), 178 (18), 163 (8), 150 (39), 135 (22), 121 (14), 109 (15), 96 (14), 77 (13), 65 (28), 55 (18), 45 (39). **4a** ; ^{13}C NMR : 206.13 (CO), 146.85 (C quat.), 139.76 (C quat.), 130.81 (CH), 129.57 (CH), 128.45 (CH), 119.27 (CH), 46.56 (CH), 41.30 (CH_2), 35.55 (CH), 27.93 (CH_2), 24.90 (CH_2), 23.11 (CH_2). MS : m/z (EI) : 186 ($M^{+\cdot}$, 82), 185 (25), 158 (47), 130 (98), 115 (100), 102 (8), 89 (13), 77 (15), 63 (17), 51 (9).

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