Oxymercuration-demercuration of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydro-1,3-pentalenedimethanol Dibenzoate

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Oxymercuration of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydro-1,3-pentalenedimethanol dibenzoate ***1*** *was performed with mercuric tetrafluoroborate alone, in the presence of tetrafluoroboric acid and with tetrafluoroboric acid + sodium acetate and demercuration with sodium borohydride in 3N NaOH. The hydration of the alkene was selective toward the symmetric alcohol at short time, but at prolonged time, the symmetric and un-symmetric alcohols were obtained in a near 1:1 ratio. Anyway, the oxymercuration-demercuration of alkene* ***1*** *is a slow hydration reaction.*

Keywords: Oxymercuration-demercuration; mercuric tetrafluoroborate; mercuric acetate; hexahydro-1,3-pentalenedimethanol dibenzoate; octahydropentalene-triols

Carbacyclin and isocarbacyclin analogues became recognized drugs, mainly with antitrombotic activity: Iloprost [1], Ciprostene [2], Eptaloprost [3], Cicaprost [4], Naxaprostene [5], Clinprost [6], (fig. 1).

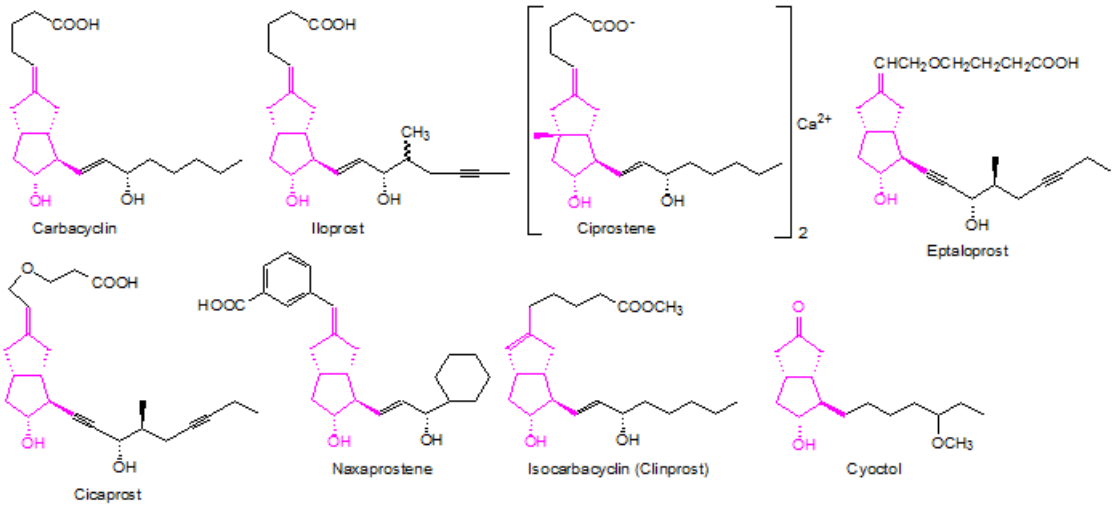
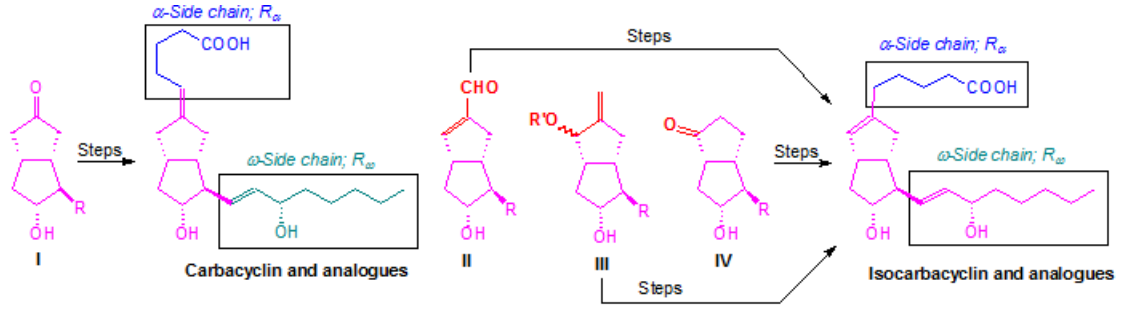


Fig. 1.

Other analogues arrived in different clinical phases of research, like compounds [7].

The above compounds are characterized by a key hydrogenated pentalenofuranic fragment, on which are linked the two side chains, α and ω, like in the prostaglandins. A pentalenofuranic synthon is found also in the Cyoctol drug [8] and in different antibacterial [9] and antitumor natural products, like in (—)-Coriolin [10a], Suberosenone [10b], etc.

The building of the (iso)carbacyclin analogues is based on a convergent strategy in which three key intermediates are synthesized, *one for linking the* ω*-side chain* in a *E*-stereoselective Horner-Emmons-Wardworth olefination on an aldehyde group, *one for linking the* α *side chain* by a *E*-stereoselective (against the ω-side chain) Wittig reaction on a ketone group and *a hydrogenated pentalene intermediate*, which must have the ketone and aldehyde groups (requested for link of the α- and ω-side chains) and also the secondary hydroxyl group. The pentalene intermediate is different for carbacyclin or isocarbacyclin synthesis. For carbacyclins synthesis, a pentalene intermediate with a symmetric ketone group is used, like **I** and intermediates three intermediates are used for isocarbacyclins synthesis, depending of the linking procedure of the α-side chain, **II**, **III** and **IV** (scheme 1, partially presented in [11]).



Scheme 1. Key intermediates for synthesis of carbacyclin and isocarbacyclin analogues

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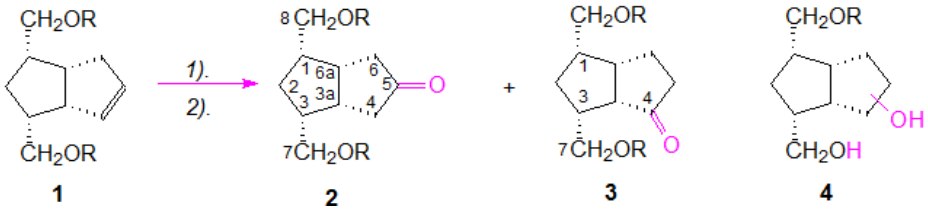


Scheme 2. Synthesis of the ketone-octahydropentalene intermediates **2** and **3** from the alkene **1**, by hydroboration-oxidation to alcohols, followed by their PDC oxidation [11]

For obtaining new carbacyclin and isocarbacyclin analogues, was developed a procedure for hydroboration of (±)-(1α,3α,3aβ,6aβ)-1,2,3,3a,4,6a-hexahydro-1,3-pentalenedimethanol and its O-acylated (Benzoate and acetate) derivatives **1** [11], an anti-Markovnikov hydration of alkenes, to obtain the key intermediates **2** and **3** (scheme 2).

The alcohols obtained by hydroboration-oxidation of alkene **1** were obtained in generally in 1:1 ratio. The ratio of the alcohols was changed to > 2:1 unsymmetric alcohol/symmetric alcohol by increasing the reaction temperature and also, by increasing the reaction mixture, due to isomerization of the borane intermediates, before their oxidation to the alcohols. In case of benzoate and acetate esters of alkene **1**, together with the corresponding symmetric and unsymmetric alcohols, about 38% of the triol-ester **4** was also obtained, due to the reduction of the closer ester group to the double bond by forming an internal borane intermediate.

In the present paper, we tried to obtain the symmetric and un-symmetric alcohols by a Markovnikov oxymercuration reaction of the double bond of **1**, followed by reduction of the organomercuric intermediates, and the results are presented below.

The alkene **1** was obtained as previously we published [12]; the alkene was already used to obtain *pseudo-carbacyclin* type compounds [13] or transformed the double bond into a diol by $KMnO_4$ hydroxylation [14], into epoxides by MCPB epoxidation [15] and in regio-selective reactions [16].

Experimental part

The progress of the reactions was monitored by TLC on silica gel $60F_{254}$ plates (Merck) in solvent systems: I (benzene-ethyl acetate-hexane, 5:3:2), II (cyclohexane-ethyl acetate, 5:1), III (ethyl acetate-methanol-acetic acid, 90:13:1), IV (acetone-hexanes, 2:1), V (hexane-ethyl acetate-acetic acid, 5:3:0.1), VI (hexane-ethyl acetate-acetic acid, 5:3:0.1), VII (ethyl acetate-hexane-acetic acid, 5:1:0.1). Spots were visualized in UV or with 15% H_2SO_4 in MeOH (heating at 110°C, 10 min). The compounds were purified by low pressure chromatography (< 2 atm) (LPC), on a glass column, in the solvent systems presented at experimental. IR spectra were recorded on an FT-IR-100 Perkin Elmer spectrometer and frequencies are expressed in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 BB spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C). IR and NMR spectra of the alcohols **7** and **8** are in agreement with the previously presented data [11].

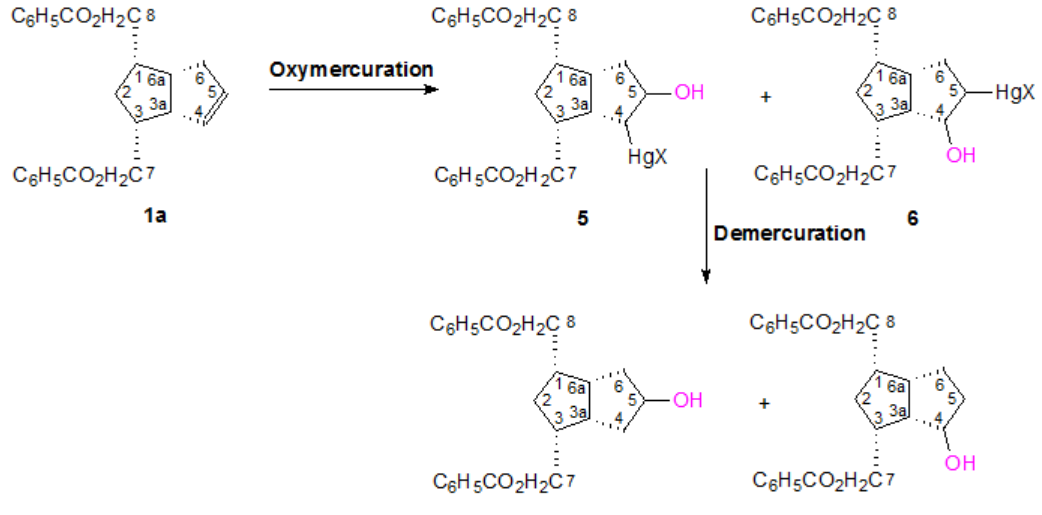
*Oximercuration-demercuration of 2α,4α-dimethanol-18,5β- bicyclo[3.3.0]octene-6 dibenzoate with mercuric tetrafluoroborate in a ratio: **1**/Hg(BF$_4$)$_2$, 2:1.0*

The oxymercuration reagent, mercuric tetrafluroborate, was obtained by reaction of red HgO (2.38 g, 11 mmole) with 44.3% (g/v) HBF_4 (3.52 mL, 22 mmole), under stirring for 2h at r.t. [21].

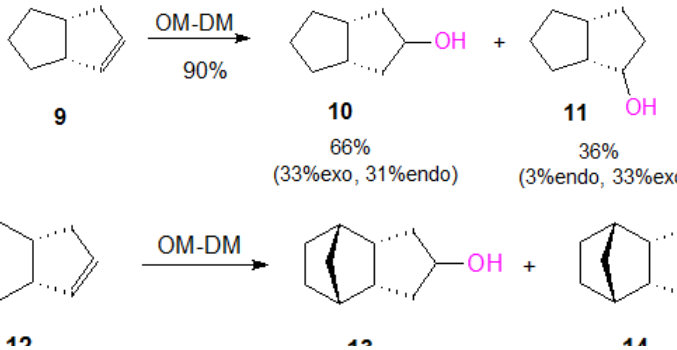
To a solution of $Hg(BF_4)_2$ (2 mmol), water (3 mL) and THF (2 mL) were added a solution of dibenzoate **1** (376 mg, 1 mmol) in THF (1 mL) was added and stirred over weekend (3 days), monitoring the evolution of the reaction by TLC (benzene-ethyl acetate-hexane, 5:3:2, Rf_1 = 0.83, Rf_7 = 0.45, Rf_8 = 0.33). The reaction mixture was diluted with ethyl ether (5 mL), cooled on an ice-bath, 3M NaOH (2 mL) and 0.5M $NaBH_4$ in 3M NaOH (4 mL) were added dropwise in the same time, the stirring was continued for 10 min., the phases were separated and the aqueous phase extracted with 30 mL ethyl ether. The unified organic phases were washed with sat. soln. NH_4Cl (20 mL), dried ($MgSO_4$), filtered, concentrated and the crude product (0.78 g) was purified by LPC, resulting the symmetric alcohol **7** and un-symmetric alcohol **8**, with the same characteristics with that previous published [11], in the ratio presented in table 1.

*Oximercuration-demercuration of 2α,4α-dimethanol-18,5β- bicyclo[3.3.0]octene-6 dibenzoate with mercuric tetrafluoroborate in a ratio: Hg(BF$_4$)$_2$/**1**, 2:1 and HBF$_4$.*

To a solution of $Hg(BF_4)_2$ (2 mmol), 44.3% HBF_4 (0.1 mL, 0.5 mmol), water (1 mL) and THF (4 mL), a solution of of dibenzoate **1** (376 mg, 1 mmol) in THF (1 mL) was added and stirred for 4 days (after 24 h the ratio of **7**/**8** was ~ 3:1). The reaction mixture was worked-up as previously and



Scheme 3. Oxymercuration-demercuration of alkene 1a



Scheme 4. Oxymercuration-demercuration of alkene 9 [18]

Entry	Oxymercuration reagent [17, 18][11,12]	Yield (%)	Time	**13** (%)	**14** (%)
1	$Hg(OAc)_2$	36	7.5 days	75	25
2	$Hg(OAc)_2$ + HX X= TsOH, $HClO_4$, etc.	50-70	20 h		
3	$Hg(O_2CCF_3)_2$	62	3 h	81	19

Scheme 5. Oxymercuration-demercuration of alkene **12**

Table 1

OXYMERCURATION-DEMERCURATION OF ALKENE 1

Entry	$Hg(BF_4)_2$	HBF_4	NaOAc	Alkene **1**	Time (Days)	THF / water	**7/8**	**7** (%)	**8** (%)	Total yield (%)
1	*2*	-	-	*1*	*3*	*1:1*	*6.9/1*	*18.5*	*2.7*	*21.2*
2	2	-	2	1	3	1:1	3.9/1	36.8	9.4	46.2
3	2	0.5	-	1	4.2	1.7:1	1.25/1	38.9	31.1	70.0
4	3	-	3	1	3	1:1	4.1/1	62.7	15.3	78.0
5	3	0.56	3	1	1	1.7:1	3.3/1	49.9	15.1	65.0
6	3	0.56	3	1	38	2.5:1	1/1.4	34.2	47.8	82.0

the crude product was purified by LPC; the results are presented in table 1 (entry 3).

*Oximercuration-demercuration of 2α,4α-dimethanol-18,5β- bicyclo[3.3.0]octene-6 dibenzoate with mercuric tetrafluoroborate in a ratio: $Hg(BF_4)_2$ / **1**, 3:1 in the presence of 3 equivalents of sodium acetate.*

To a solution of $Hg(BF_4)_2$ (3 mmol), AcONa (246 mg, 3 mmol), water (3 mL) and THF (2 mL), a solution of dibenzoate **1** (376 mg, 1 mmol) in THF (1 mL) was added and stirred for 3 days at r.t (over weekend). The reaction mixture was worked-up as previously and the crude product was purified by LPC; the results are presented in table 1 (entry 4).

*Oximercuration-demercuration of 2α,4α-dimethanol-18,5β- bicyclo[3.3.0]octene-6 dibenzoate with mercuric tetrafluoroborate in a ratio: $Hg(BF_4)_2$ / **1**, 3:1 in the presence of 3 equivalents of sodium acetate and 0.6 equivalents of HBF_4.*

To a solution of $Hg(BF_4)_2$ (3 mmol), HBF_4 (0.096 mL, 0.6 mmol), AcONa (246 mg, 3 mmol), water (2 mL) and THF (4 mL), a solution of dibenzoate **1** (376 mg, 1 mmol) in THF (1 mL) was added and stirred for 38 days at r.t. The reaction mixture was worked-up as previously and the crude product was purified by LPC; the results are presented in table 1 (entry 6).

Results and discussions

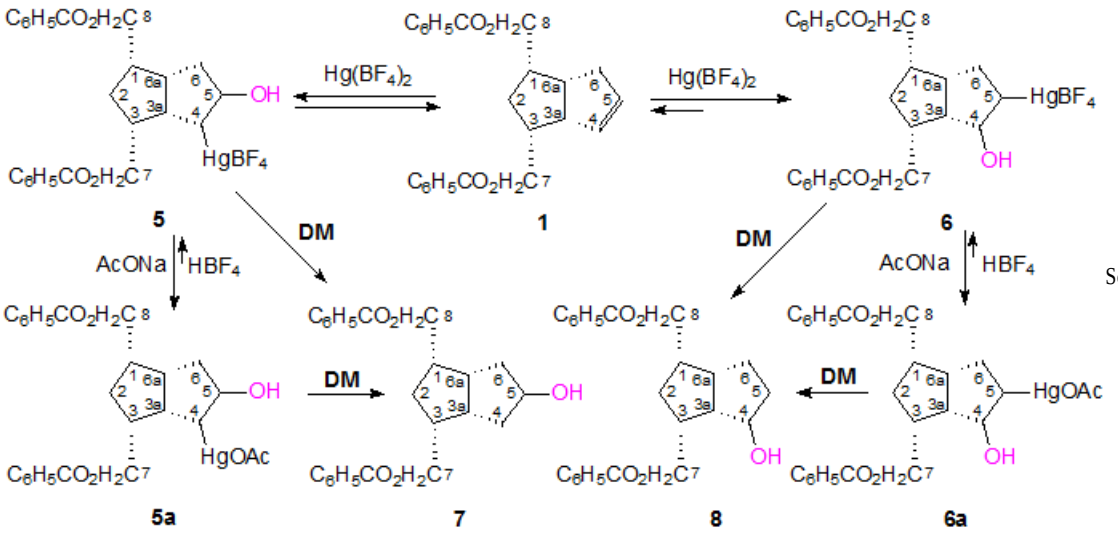
If in the previous paper [11] the hydration was performed by a hydroboration-oxidation reaction, an anti-Markovnikov hydration of alkenes, in this paper we present the hydration of the double bond of compound **1** by an oxymercuration-demercuration (OM-DM) reaction, which is an opposite anti-Markovnikov reaction.

Browsing the literature, we find that for terminal alkenes, the hydration links the hydroxyl to the C_2 and HgX to C_1, giving a secondary alcohol [17]. In the case of internal di-substituted alkenes (R-CH=CH-R'), the reaction is strongly influenced by steric factors, the hydroxyl group being preferential linked to the less sterically constrained carbon atom and *cis*-alkenes react more rapidly than *trans*-alkenes [17]. In this point of view, in the alkene **1**, with a *cis*-internal double bond, in which the C_4 is linked to a bis-substituted carbon atom (C_{3a}) and C_5 is linked to a mono-substituted carbon atom (C_6), the OM-DM will give sure a mixture of the alcohols **7** and **8**, but the symmetrical alcohol **7** should be favoured in detriment of the un-symmetric alcohol **8** (scheme 3).

Previously, by OM-DM of alkene **9**, the symmetric alcohol **10** was obtained in about two times quantity than the un-symmetric alcohol **11** [18] (scheme 4).

Browsing the literature, we found that in the case of the more constricted tricyclic alkene **12**, OM-DM with $Hg(OAc)_2$ is not a rapid reaction (scheme 5) [17, 18].

In the presence of an acid, the speed of OM reaction is considerably increased and the yield is also increased (entry 2). With mercuric trifluoroacetate, the speed of reaction and the yield were increased (entry 3) [17,18]. Canceller et al [19] observed the same effect by using mercuric tetrafluoroborate for OM of the double bond of the mixture



Scheme 6.Isomerization of organomercuric intermediates during OM-DM

of 5- and 6-hydroxy 3a,4,5,6,7,7a-hexahydro-1H-4,7-methanoinden.

First, we used mercuric acetate for OM of alkene **1**, but <10% alcohols were obtained after 6 days. With one equivalent of TsOH the yield increased to ~20% (TLC, densitometric).

Then we used mercuric tetrafluoroborate, prepared in situ from red HgO and 40-50% tetrafluoroboric acid [19, 20] and OM was performed in the conditions presented in the literature [19]. With a ratio of 2:1 OM reagent/alkene **1**, the yield was 21.2%, but the symmetric alcohol was obtained selectively, 6.9/1 (**7**/**8**) (table 1). By performing the OM with 2 equivalents reagent excess and *in the presence of 2 equivalents of NaOAc*, the yield was increased to 46.2% and selectivity was reduced to 3.9/1 (**7**/**8**, entry 2). With greater excess, *3/3/1, $Hg(BF_4)_2$/AcONa/ alkene **1***, the yield was increased to 78% at about the same selectivity (entry 4). Knowing that an acid added to the OM reagent increase the yield [17, 18], we add 0.4 equivalent of HBF_4 and two equivalents of $Hg(BF_4)_2$/ alkene, the yield was significantly increased to 70%, but the selectivity was reduced to 1.25/1 (**7**/**8**, entry 3). Reducing the time of reaction to one day and slightly increase the acid to 0.56 equivalents, the selectivity was maintained to 3.3/1 (**7**/**8**, entry 5). Increasing the reaction time to 38 days, the selectivity for alcohols was inversed in the favour of un-symmetric alcohol (1:1.4, **7**/**8**, entry 6).

The results presented above strengthens the literature data [17, 18] that the OM is a reversible reaction and that HBF_4 acid increase not only the speed of reaction, but also catalyze the isomerization of the probably kinetically formed organomercuric intermediate **5**, to the thermodynamically more stable **6** (a proposed mechanism is presented in scheme 6).

By transformation of the organo-fluoroborate intermediates **5** and **6**, initially formed, to the more stable organo-acetate intermediates **5a** and **6a**, sodium acetate shifts the equilibrium of the isomerization reactions toward the **5a** and **6a** and increase the speed of the reactions and so the yield of the products. In the same time, the selectivity toward the symmetrical alcohol is decreased.

The reduction of the organomercuric intermediates **5** and **6** (and also of **5a** and **6a**) to the alcohols **7** and **8** are quickly performed with sodium borohydride in the presence of sodium hydroxide, as usually.

In cases where sodium acetate was used, a more polar byproduct was obtained in ~10% yield which I suppose that is a mono-acylated triol, by deprotection of a benzoate group, as we observed in hydroboration-oxidation of **1** [11].

The unprotected alkene **1b** (R = CH_2OH) could not be used in OM-DM, because in this case there is a selective participation of the closer hydroxymethyl (linked to C_3) to the double bond in the reaction with the formation of a pentalenofurane compound, as previously we described [16].

So, the synthesis of the alcohols **7** and **8** could be selectively oriented toward the symmetrical alcohol **7** or, by increasing the reaction time, toward the un-symmetrical alcohol **8**.

The following of the reaction in time was also studied by HPLC and the results will be presented in a separate paper.

Conclusions

Oximercuration-demercuration, as an alternative to the hydroboration-oxidation hydration of alkene **1**, was realized. The oxymercuration-demercuration goes slowly due to the steric constrictions of the molecule. At a ratio of $Hg(BF_4)_2$/**1** of 2:1 for 3 days, the yield is slow and the symmetric alcohol is moderate selectively obtained. The yield was improved by adding HBF_4 or as acid catalyst. In the presence of sodium acetate, the yield was also improved. In both cases, the selectivity for symmetric alcohol was slowly reduced, but remains at a level near to 4:1 (**7**/**8**). In time, for ex. in 38 days, the selectivity was reversed to the un-symmetric alcohol **8**: **8**/**7** = 1.4:1. By manipulation of the reaction conditions, the selectivity was conducted to symmetric alcohol (**7**) or un-symmetric alcohol (**8**).

References

1.a) SKUBALLA, W., SCHILLINGER, E., STURZEBECHER, C., VORBRUEGGEN, H. J. Med. Chem. **29**, 1986, p. 313; b) SKUBALLA, W., VORBRUEGGEN, H. Angew. Chem., Int. Ed. Engl. **20**, 1981, p. 1046; c) SKUBALLA, W., RADUCHEL, B., VORBRUEGGEN, H., in Prostacyclin and its stable analogue Iloprost, R. J. Griglewski and G. Stock Eds, Springer-Verlag, Berlin, Heidelberg, 1987.

2.a) ARISTOF, P. A., JOHNSON, P. D., HARRISON, A. W. J. Org. Chem., 1983, **48**, no 26, p. 5343-5348; b) Shirotani M, Yui Y, Hattori R, Kawai C. Prostaglandins. 1991, **41** no 2, p. 97-110; c) CRASTO, A., Drugs Fut. 1985, 10 no 11, p. 900.

3.a) CONSTANTINI, V., GIAMPIETRI, A., ALLEGRUCCI, M., AGNELLI, G., NENCI, G. G., FIORETTI, M. C., Adv. Prostaglandin, Thromboxane, Leukotriene Res. **21B**, 1991, p. 917; b) SCHNEIDER, M. R., SCHILLIGER, E., SCHIRNER, E., SKUBALLA, W., STURZEBECHER, S., WITT, W., Adv. Prostaglandin, Thromboxane, Leukotriene Res. **21B**, 1991, p. 901; c) SKUBALLA, W., RADUCHEL, B., VORBRUGGEN, H.,

CASALS-ETENZEL, J., MANNESMANN, G., SCHILLINGER, E., TOWN, M.-H., DE 3226550/1994.
4. LERM, M., GAIS, H. J., CHENG, K., VERMEEREN, C. J. Am. Chem. Soc., 125 no 32, **2003,** p 9653.
5.WINTER, W. Drugs Fut. **15** no, 3, 1990, p. 233.
6.a) CROATT, M., US 2014/0114086 A1, Apr. 24, 2014; b) NAGY, E. E., HYATT, I. F. D., GETTYS, K. E., YEAZELL, S. T., FREMPONG, S. K. Jr., Croatt, M. P. Organic Letters **2013**, **15**, p. 586-589.
7.KANOYAMA, T.; KIMURA, Y.; ISEKI, K.; HAYASHI, Y.; TAMAO, Y.; MISOGAMI, S. Antithrombotic effects of KP-10614, a novel and stable prostacyclin (PGI2) analog. J. Pharmacol. Exp. Ther. 1990, **255**, p. 1210–1217; b) KANAYAMA T., KIMURA Y., MIZOGAMI S. J. Pharmacol. Exp. Ther. 1990, **266** no 1, p. 344-349.
8.WIECHERS, J. W., HERDER, R. E., DRENTH, B. F. H., DeZEEUW, R. A. Int. J. Pharm. **65**, 1990, p. 77.
9.NISHIDA, M., ISEKI, K., SHIBASAKI, M., IKEGAMI, S. Chem. Pharm. Bull. **38**, 1990, p. 3230.
10.a) MIZUNO, H., DOMON, K., MASUYA, K., TANINO, K., KUWAJIMA, I. Org. Lett., 2, **2000,** p. 1951.
11.TANASE, C. I., COCU, F. G., CAPROIU, M. T., DRAGHICI, C., SHOVA, S. Molecules **22**, no. 12, p. 2032.
12.TANASE, C. I., COCU, F. G., DRAGHICI, C., CAPROIU, M. T. Rev. Roum. Chim., **53** no. 3, 2008, p. 195.
13.a) TANASE, C. I., COCU, F. G., CAPROIU, M. T., DRAGHICI, C. Rev. Chim.(Bucharest) (English Edition), **52**, no. 1-2, 2001, p. 11, b) TANASE, C. I., COCU, F. G., DRAGHICI, C., CAPROIU, M. T. RO Patent 116896 B / 2001.
14.TANASE, C. I., COCU, F. G., DRAGHICI, C., CAPROIU, M. T. Rev. Roum. Chim. **53** no. 3, 2008, p. 189.
15.TANASE, C. I., DRaGHICI, C., CAPROIU, M. T., Shova, S., COJOCARU, A., MUNTEANU, C. V. A. Tetrahedron, **71** no. 24, 2015, p. 4154.
16.TANASE, C. I., DRAGHICI, C., SHOVA, S., MAGANU, M., COJOCARU, A., MUNTEANU, C. V. A., COCU, F. Tetrahedron, **71** no. 38, 2015, p. 6852.
17.BROWN, H. C., GEORGHEGAN, P. J. J. Org. Chem., **35**, 1970, p. 1844.
18.BROWN, H. C., Hammar, W. J. Tetrahedron **34**, 1978, p. 3405.
19.CARCELLER, E., GARCIA, M. L., MOYANO, A., SERRATOSA, F. Synth. Commun., **15** no. 11, 1985, p. 951.
20.BARLUENGA, J., ALONSO-CIRES, L., CAMPOS, P. J., ASENSIO, G. Tetrahedron, **40**, 1984, p. 2563.
21.BARLUENGA, J., ALONSO-CIRES, L., ASENSIO, G. Synthesis, 1979, p. 962.

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