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MOLECULAR DESIGN OF NOVEL PGI_2 AGONISTS WITHOUT PG SKELETON. III

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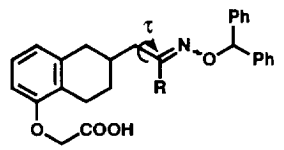
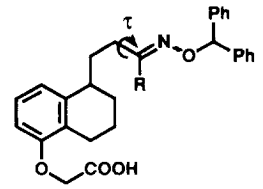
Abstract. Several ether, oxime, and amide derivatives related to **1** and **3** were synthesized and tested as PGI_2 agonists. The results reveal the importance of the orientation between carboxylic acid and terminal diphenyl groups in order to obtain high affinity interaction with PGI_2 receptors.

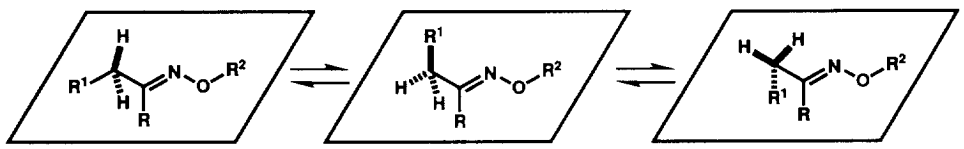
Prostacyclin (PGI_2) is a potent, short-lived and endogenous arachidonic acid derivative which induces platelet antiaggregation and vasodilation. The stabilized PGI_2 analogs have been implicated as an agent in clinical trials.[1] As part of a research program to develop clinically more useful PGI_2 agonists we have devoted ourselves to the design of stable non-PG structural PGI_2 agonists which exhibit a therapeutically useful *in vivo* duration of action in addition to high potency. We previously described the design of new PGI_2 agonists **1-4**, and among them compound **2** was an especially potent and orally active PGI_2 agonist with an extended duration of action.[2]



1 R = H
2 R = *n*-Pr



3 R = H
4 R = *n*-Pr

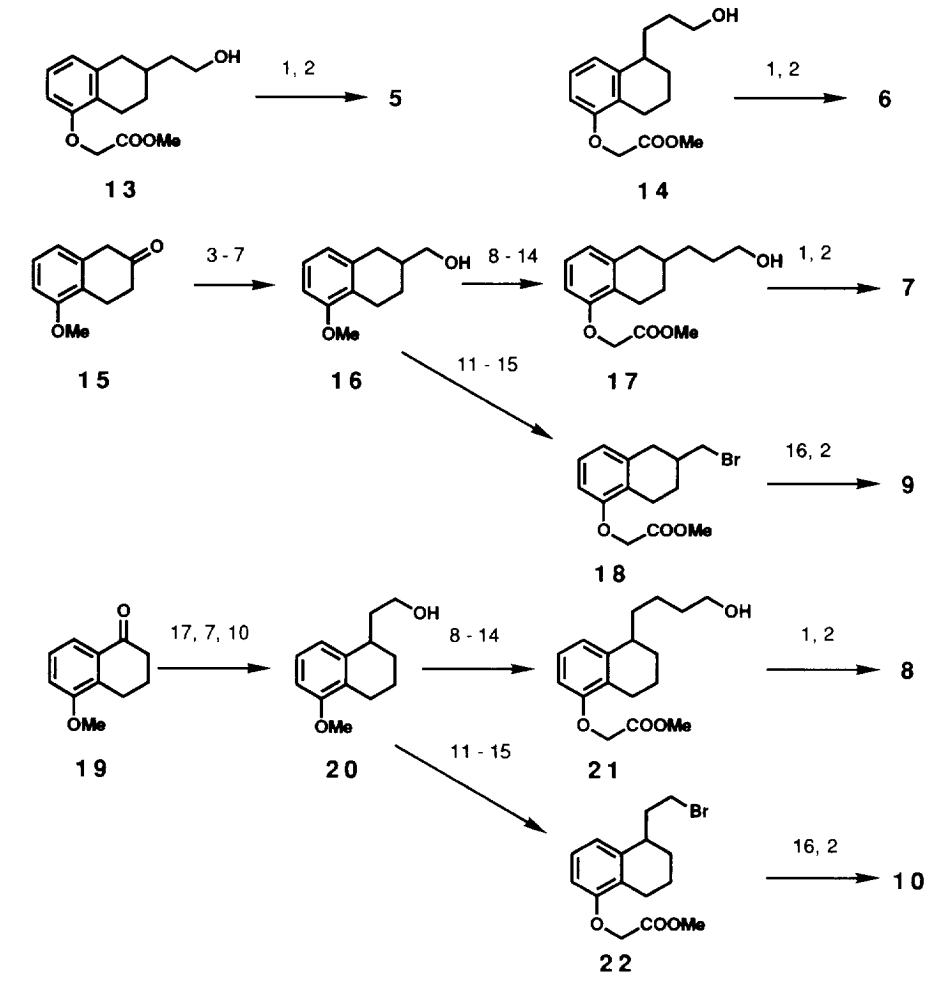


I **II** **III**

The activity of **2** would be attributed to the conformational restriction around τ, according to the previous calculations.[2] In compound **1**, rotation around τ gives three possible conformers with local energy minimum, of which one is the *anti* form between C_α-R^1 and C=N bond (**I**) and the others possess the C_α-R^1bond

perpendicular to the plane of the oxime group (**II** and **III**). In the case of **2**, there are only two conformers **II** and **III** since there exists a steric repulsion between R^1 and R^2 in **I**. This result gave the insight that the active conformers of **1** and **2** in rotation τ should be **II** and **III**. With regard to **3** and **4**, almost the same conformational phenomenon was observed as that of **1** and **2**; however, **4** was less active than **3**. This would show that the active conformer of **3** and **4** in the rotation τ should be conformer **I**. These results prompted us to search for other functional groups giving more potent binding affinity than the oxime moiety in compound **3**. We herein report the results of a systematic study to replace the oxime moiety in **3** with alternative linking groups which would afford conformer **I**, for example sp^3 carbon, oxygen, and ketone.

Scheme 1



(1) $Ph_2CHOCNHCCl_3$, BF_3·OEt_2; (2) NaOH, MeOH; (3) $NaHSO_3$; (4) NaCN; (5) $POCl_3$, pyridine; (6) DIBAL; (7) H_2, Pd-C, AcOEt; (8) Swern Ox.; (9) $Ph_3PCHCOOMe$; (10) $LiAlH_4$, THF; (11) Ac_2O, Pyridine; (12) BBr_3, CH_2Cl_2; (13) NaOH; (14) $BrCH_2COOMe$, K_2CO_3, MeCN; (15) CBr_4, Ph_3P; (16) Ph_2CNOH, *t*-BuOK, DMF; (17) Zn, $BrCH_2COOEt$, C_6H_6.

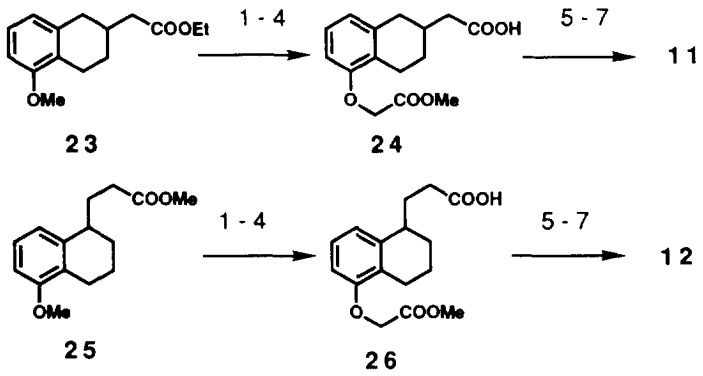
Chemistry

The compounds were synthesized by the routes shown in Schemes 1 and 2. Ester alcohols **13** and **14** were prepared by the method in our previous paper.[2] Treatment of **13** and **14** with benzhydryl trichloroacetimidate in the presence of a catalytic amount of borane trifluoride etherate gave benzhydryl ethers which were hydrolyzed to afford the acids **5** and **6**.

Conversion of **15**[3] into key intermediate **16** was achieved by (i) treatment with sodium bisulfite to give the bisulfite addition product; (ii) cyanation; (iii) dehydration with phosphorous oxychloride to the α, β-unsaturated nitrile; (iv) diisobutylaluminum hydride reduction; and (v) hydrogenation. Another key intermediate **20** was easily accessible from **19** by Reformatsky reaction followed by deoxygenation and reduction. Compounds **17** and **21** were obtained from **16** and **20**, respectively, by the following series of reactions: (i) Swern oxidation; (ii) two carbon elongation by Wittig reaction; (iii) reduction of the resulting ester with lithium aluminum hydride; (iv) acetylation; (v) demethylation; (vi) hydrolysis of the acetate; and (vii) *O*-alkylation. Ethers **7**[3] and **9** were easily prepared by the same preceding procedure.[2] Compounds **18** and **22** were obtained from **16** and **20**, respectively, in five steps. Alkylation of **18** and **22** with benzophenone oxime/sodium hydride followed by saponification gave **9** and **10**[4].

Scheme 2 illustrates the preparation of amides **11** and **12**[5]. Compounds **23** and **25** were prepared by a previously described method.[2] Conversion of **23** and **25** into the carboxylic acids **24** and **26** was accomplished by (i) deprotection of ether and ester; (ii) selective protection of the carboxylic acid; (iii) *O*-alkylation; and (4) debenzylation. Amidation of **24** and **26** with *N,N*-diphenyl hydrazine, Mukaiyama reagent, and triethylamine furnished amides which were hydrolyzed to **11** and **12**.

Scheme 2



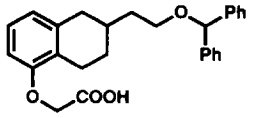
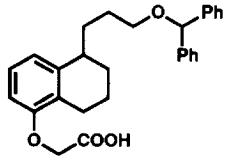
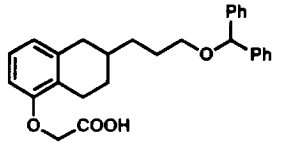
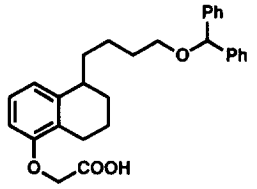
(1) HCl·Pyridine; (2) Li_2CO_3, BzlBr, DMF; (3) $BrCH_2COOMe$, K_2CO_3, MeCN; (4) H_2, Pd-C, AcOEt; (5) 2-chloro-1-methylpyridinium iodide, Et_3N; (6) NaOH, MeOH.

Biological Results and Discussion

Evaluation of PGI_2 binding was undertaken using the conventional ligand binding assay based on the displacement of [^{3}H]-iloprost from human platelets. IC_{50} values of the functional assay were obtained by measuring inhibition of 4 μM ADP-induced platelet aggregation using human platelet rich plasma.

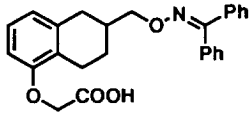
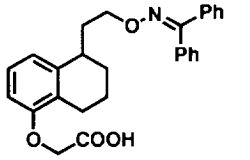
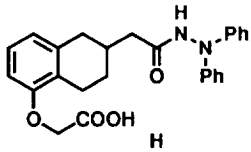
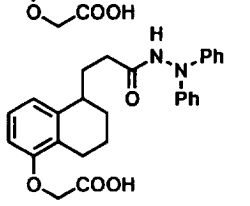
The structure-activity relationship apparent from Table 1 clearly demonstrates that the biological activities are dependent on the side chain length and the isomeric position of the side chain. 2-Substituted tetrahydronaphthalene derivative **7** having two sp^3 carbons in which C=N double bond of oxime was altered did not show affinity for the PGI_2 receptor, likewise compound **5**, shorter one methylene, bound only weakly to the PGI_2 receptors. Similarly, 1-substituted tetrahydronaphthalene derivatives **6** and **8** showed the same binding tendency as 2-substituted tetrahydronaphthalene derivatives **5** and **7**; however, compound **6** , shorter by one methylene inhibited ADP-induced human platelet aggregation with an IC_{50} of 0.45 μM. This present study showed that replacement of C=N double bond with a sp^3 carbon was effectual for 1-substituted tetrahydronaphthalene derivatives. A more likely explanation for the potent activity of ether **6** lies in the change in chain length in which one carbon is reduced compared to oxime **3**.

Table 1. The Effect of 1 or 2-Substituted Tetrahydronephthalene Derivatives with Benzhydryl Ether on the Binding and Functional Assays

No.		Binding Assay IC_{50} (μM)	Functional Assay IC_{50} (μM)
5		8.0	>20
6		0.46	0.45
7		>10 (25%)	>20
8		4.2	11

Using ether and ketone groups as a probe to examine the influence of binding or functional assays, a series of oxime and amide analogs were evaluated as shown in Table 2. 2-Substituted tetrahydronaphthalene oxime **9** did not significantly affect binding with an IC_{50} of 2.4 μM; however, 1-substitution resulted in a 10-fold increase in affinity (**10**, IC_{50} = 0.21 μM) and antiaggregative activity (IC_{50} = 0.25 μM). When *N,N*-diphenylhydrazine amide group occupies the 2 position (**11**), an additional 10-fold increase in binding potency was achieved and biological activity was improved. Moreover, occupation of the 1 position afforded a 2-fold increase in affinity (**12**, IC_{50} = 0.01 μM) and a 3-fold increase in antiaggregative activity (IC_{50} = 0.057 μM), **12** was equipotent with PGE_1 in antiaggregatory activity.

Table 2. The Effect of 1 or 2-Substituted Tetrahydronephthalene Derivatives with Oxime and Amide on the Binding and Functional Assays

No.		Binding Assay IC_{50} (μM)	Functional Assay IC_{50} (μM)
9		2.4	2.4
10		0.21	0.25
11		0.02	0.15
12		0.01	0.057

Our previous report[2] suggested that the active conformer of **3** around τ should be conformer **I**, and the active one of **1** should be conformer **II** or **III**. According to this postulation, we designed compounds that would have **I** as the major conformer. Consequently, 1-substituted tetrahydronaphthalene derivatives with ether **6**, oxime **10**, and amide functions **12** showed potent activity as PGI_2 agonists in spite of its varieties of the

linking groups. Moreover, this result revealed the importance of the orientation between carboxylic acid and terminal diphenyl groups in order to obtain highly active PGI_2 agonists.

References and Notes

1. Iloprost: Schillinger, E.; Vorbuggen, H. C.. *Drugs Future*, **1981**, *6*, 676. Beraprost (TRK 100): *ibid.*, **1986**, *11*, 956. *ibid.*, **1990**, *15*, 1118.
2. For Part II, see: Hamanaka, N.; Takahashi, K.; Nagao, Y.; Torisu, K.; Takada, H.; Tokumoto, H.; Kondo, K. *Bioorg. Med. Chem. Lett.*, preceding paper in this issue. .
3. Characterization of **7**: white amorphous solid; IR (KBr): 2932, 1741, 1579, 1455, 1247, 1096 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.4-7.2 (10 H, m), 7.08 (1 H, t, *J* = 8 Hz), 6.85 (1 H, d, *J* = 8 Hz), 6.55 (1 H, d, *J* = 8 Hz), 5.34 (1 H, s), 4.65 (2 H, s), 3.48 (2 H, m), 2.9-2.5 (3 H, m), 2.0-1.6 (8 H, m); 125 MHz ^{13}C-NMR ($CDCl_3$) δ 173.26, 154.94, 143.29, 142.47, 128.29, 127.29, 126.91, 126.89, 125.62, 122.47, 107.89, 83.68, 69.33, 65.05, 37.44, 33.08, 27.74, 26.68, 23.19, 18.79; MS (FAB, Pos.) *m/z* 431 ($M+H^+$).
4. Characterization of **10**: white powder, 144-145° (ethyl acetate-hexane); IR (KBr): 2936, 1703, 1582, 1463, 1232, 1124 cm^{-1}; 200 MHz ^{1}H-NMR ($CDCl_3$) δ 7.6-7.2 (10 H, m), 7.05 (1 H, t, *J* = 8 Hz), 6.80 (1 H, d, *J* = 8 Hz), 6.53 (1 H, d, *J* = 8 Hz), 4.65 (2 H, s), 4.30 (2 H, t, *J* = 6 Hz), 3.0-2.5 (3 H, m), 2.2-1.6 (6 H, m); 125 MHz ^{13}C-NMR ($CDCl_3$) δ 173.13, 156.60, 154.98, 142.92, 136.58, 133.48, 129.23, 129.16, 128.69, 128.20, 128.00, 127.83, 126.39, 125.74, 122.66, 108.00, 72.80, 65.04, 35.98, 34.50, 26.81, 23.06, 18.50; MS (FAB, Pos.) *m/z* 430 ($M+H^+$).
5. Characterization of **12**: white powder, 199-201° (ethyl acetate); IR (KBr): 3278, 2936, 1709, 1667, 1591, 1497, 1232 cm^{-1}; 200 MHz ^{1}H-NMR (d6-DMSO) δ 10.52 (1 H, s), 7.40-6.90 (11 H, m), 6.77 (1 H, d, *J* = 8 Hz), 6.59 (1 H, d, *J* = 8 Hz), 4.62 (2 H, s), 2.80-2.50 (3 H, m), 2.28 (2 H, t, *J* = 7 Hz), 1.95 (1 H, m), 1.90-1.50 (5 H, m); 125 MHz ^{13}C-NMR (d6-DMSO) δ 171.54, 170.28, 155.17, 145.73, 141.58, 128.93, 125.67, 125.17, 121.95, 121.05, 118.55, 107.99, 64.65, 36.40, 31.66, 31.18, 26.02, 22.86, 18.35; MS (EI) *m/z* 444 (M^+).

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