Tetrahedron 77 (2021) 131740

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Convenient approach for the synthesis of ONO-LB-457, a potent leukotriene B_4 receptor antagonist

Salha Hamri [a, d], Jabrane Jouha [a, c], Asmaa Oumessaoud [a, b], M.D. Pujol [b, *], Mostafa Khouili [a, **], Gérald Guillaumet [c, ***]

[a] Laboratoire de Chimie Organique & Analytique, Université Sultan Moulay Slimane, Faculté des Sciences et Techniques, BP 523, 23000, Béni-Mellal, Morocco
[b] Laboratori Química Farmacèutica, Facultat de Farmàcia, 08028, Barcelona, Universitat de Barcelona, Spain
[c] Institut de Chimie Organique et Analytique, Université D'Orléans, UMR-CNRS 7311, BP 6759, Rue de Chartres, 45067, Orléans, Cedex 2, France
[d] Laboratoire de Chimie Organique, Organométallique et Valorisation des Substances Naturelles, Faculté des Sciences, Université Ibn Zohr, BP 8106, Cité Dakhla, Agadir, 80000, Morocco

ARTICLE INFO

Article history:
Received 4 September 2020
Received in revised form
23 October 2020
Accepted 31 October 2020
Available online 17 November 2020

Keywords:
5-Hydroxychroman-2-one
5-Bromovaleric acid
Knoevenagel
Wittig reaction
Leukotriene B_4
ONO-LB-457
Inflammatory

ABSTRACT

This study reports a new approach for the synthesis of 5-[2-(2-carboxyethyl)-3-[6-(4-methoxyphenyl)-(5*E*)-hexen-1-yloxy]phenoxy]pentanoic acid **V** (ONO-LB-457), previously described by Konno and col. and which is considered a highly potent and orally active LTB_4 receptor antagonist. This compound acts as an inhibitor of aggregation and chemotaxis, in addition to LTB_4-induced human neutrophil degranulation.

In this work, the preparation of ONO-LB-457 was proposed through a convergent synthesis focused on the preparation of two fragments. First, the preparation of 5-hydroxychroman-2-one (**4**) from 2,6-dimethoxybenzaldehyde and malonic acid, involving a Knoevenagel reaction, followed by a reduction of the olefin and intramolecular cyclization catalyzed by Lewis acid (tribromide) was achieved with an overall yield of 57%. Second, preparation of (*E*)-6-(4-methoxyphenyl)hex-5-en-1-yl-methanesulfonate (**18**) from 5-bromovaleric acid (**15**) involving a Wittig reaction. The desired compound **V** (ONO-LB-457) was obtained by nucleophilic substitution of (*E*)-6-(4-methoxyphenyl)hex-5-en-1-yl-methanesulfonate (**18**) with the ring-opened phenolic diester **14** followed by hydrolysis, in seven steps with an overall yield of about 11%.

1. Introduction

Inflammation is a defense reaction of living beings to injury or excessive or abnormal cell stimulation.

It can result from trauma, burns, radiation or penetration of external pathogens (viruses, bacteria, parasites, antigens) or self-antigens (molecules inducing autoimmune antibodies) [1–6]. In the latter case, the organism is attacked by its own immune system. An inflammatory immune response involves cells participating in the immune response (reactive T lymphocytes, helper, suppressor and T4, T8 cells) but also the production of cellular mediators (cytokines) that cannot be eliminated or inhibited sufficiently quickly [7–9]. These cytokines, by following the steps of acute or chronic inflammation, can lead to the synthesis of inhibitors or activators that have a feedback effect on the inflammatory process.

In 1980, the team of Samuelsson described a group of mediators of inflammation called leukotrienes (LT) [10–12]. Recently, research was conducted on one of these inflammation mediators, namely, the leukotriene LTB_4, which is a potent activator and chemotactic for leukocytes. It is involved in many allergic and inflammatory diseases, such as allergic pulmonary inflammation, mycobacterial infections and tuberculosis susceptibility [13].

This powerful pro-inflammatory lipid derived from arachidonic acid via the action 5-lipoxygenase and an activator of leukocytes, particularly granulocytes and T cells, is mediated by two G-coupled protein receptors, BLT_1 and BLT_2, high- and low-affinity receptors, respectively (Fig. 1) [14].

Previous works describe the role of LTB_4 in the development of

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail address: mdpujol@ub.edu (M.D. Pujol).

https://doi.org/10.1016/j.tet.2020.131740
0040-4020/

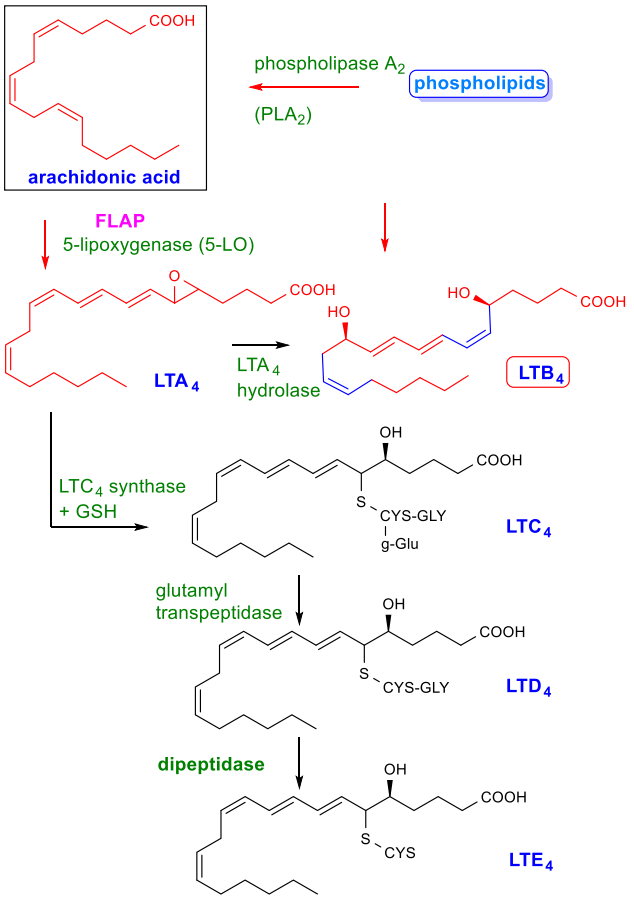


Fig. 1. Biosynthetic pathway of leukotrienes (LTs). PLA_2: phospholipase A_2; FLAP: five-lipoxygenase activating protein; 5-LO: 5-lipoxygenase; GSH: glutathione.

airway hyper-responsiveness, severe asthma and exacerbation of asthma [15–18].

Several studies have demonstrated that leukotrienes (LT), either cysteinyl LT (CysLT) or LTB_4, are important lipid mediators in the pathophysiology of asthma phenotypes. They identified at least two receptor subtypes for CysLTs-$CysLT_1$ and $CysLT_2$.

Several antagonists of LTB_4 receptors, with various biological activities, have been reported in the literature [19–26]. Among these compounds was SC-41930 an LTB_4 antagonist with multiple biological activities (IC_{50} = 300 nM). Goodnow et al. (see Fig. 2) cited other compounds such as BIIL-284, which inhibit the action of LTB4 on BLT1 and/or BLT2 [19].

All these compounds have entered clinical trials for various indications, such as inflammatory diseases and cancers.

According to a structure-activity study carried out using the conformers of leukotriene B_4, joining the carbon atoms C7 and C9 of the conformer (A) into an aromatic ring system led to the discovery of benzene analog **I** (IC_{50} = >1.0 μM) (Fig. 3) [27].

The compound **I** showed a high affinity for rat neutrophil LTB_4 receptors, but a low affinity for human neutrophils. Further investigations showed that replacing the aliphatic unit of C-4 to C-9 by an aromatic ring (conformer B) leads to the compound **II**, which is a potent antagonist of human neutrophil LTB_4 receptors (IC_{50} = 0.18 μM).

Structural analogues of leukotriene B_4 have very interesting pharmacological properties, and are the target of a series of synthetic approaches.

The introduction of a side chain carrying an amide function on

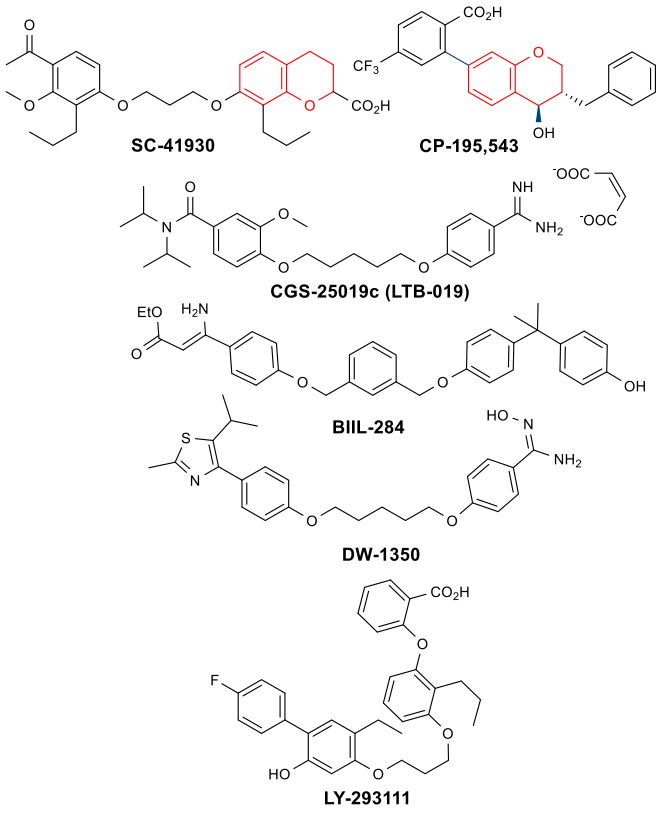


Fig. 2. Structures of antagonists of LTB_4 receptors described in the literature as molecules that have entered clinical trials [19].

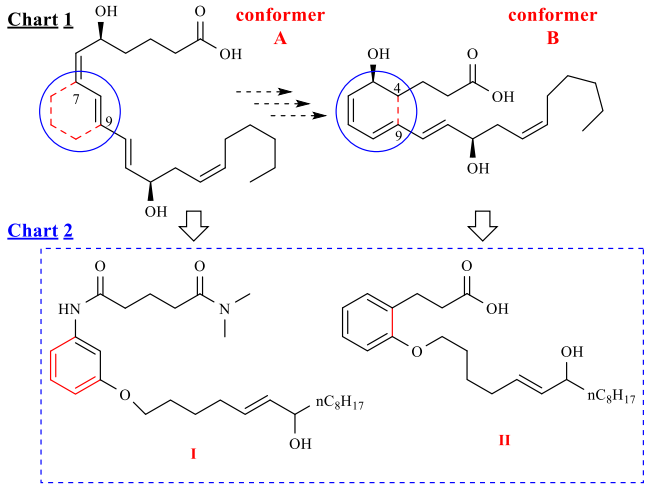


Fig. 3. Chart 1: Possible conformers of LTB_4/Chart 2: Partial stiffening of conformers **A** and **B**.

the aromatic ring of compound (**II**) in the *meta* position relative to the propionic acid chain and replacing the allyl alcohol group by *para*-methoxystyrene provides compound (**III**) which is a potent LTB_4 receptor antagonist (IC_{50} = 0.09 μM).

The grafting of the side chain in the *ortho* propionic part, rather than *meta*, yields the derivative *ortho* **IV** (ONO-LB-448), whose activity is six times greater than that of **III**.

Unfortunately, *in vivo*, and administered orally, compound **III** has an extremely short duration of action, whereas the carboxylic

acid **V** (ONO-LB-457) has an activity comparable to that of compound **IV** (ONO-LB-448), with sustainable action *in vivo*, and it is the most promising compound of the entire series (Fig. 4).

In this report, we describe the synthesis of analogue **V** (ONO-LB-457) that has a strong affinity to the LTB_4 receptor.

This compound can be considered a lead as an antagonist of the LTB_4 receptor. New structural modifications should allow optimizing its anti-inflammatory capacity.

2. Results and Discussion

The synthesis of ONO-LB-457 in eight steps from 1,3-cyclohexanedione and ethyl acrylate was described, though without analytical details, in the patent by Konno et *al.* (Scheme 1) [20].

This sequence involves a Michael reaction and aromatization of the enol-acetate derivative, followed by a cyclization reaction, thereby providing a 5-hydroxy-chroman-2-one intermediate (**4**).

Therefore, a simple nucleophilic attack of the phenoxide moiety on the mesylate derivative leads to the formation of (*E*)-5-((6-(4-methoxyphenyl) hex-5-en-1-yl)oxy)chroman-2-one (**5**), then the opening of the heterocyclic system gives the *O*-substituted phenol ester derivative at the C-6 position of the aromatic ring, (*E*)-ethyl 3-(2-hydroxy-6-((6-(4)methoxyphenyl)hex-5-en-1-yl) oxy)phenyl) propanoate (6).

This intermediate **6** undergoes a second substitution, this time, with the ethyl 5-bromovalerate motif, giving ONO-LB-457, as described in the patent after a last saponification step (Scheme 1).

Another strategy for the synthesis of 5-hydroxychroman-2-one (**4**) from 1,3-cyclohexanodione (**1**) and ethyl acrylate, in three steps with an overall yield of 41%, was reported in 2013 by Sharma's team [28] (Scheme 2).

In order to fine-tune the synthesis of the LTB4 receptor antagonists, we initially focused on the preparation of the ONO-LB-457 itself, required as a reference for the desired biological tests.

At first, an attempt was made to reproduce the synthesis described by Konno et al. starting from 1,3-cyclohexanedione [20a] with the aim of obtaining compound **V**: ONO-LB-457. However, the first step of adding cyclohexanedione to ethyl acrylate led to a mixture of the expected ester and the diester product of the double Michael addition. Starting with small amounts of cyclohexanone, the use of NaH as a base offers better results than sodium ethoxide, but on a multigram scale, a crude reaction difficult to purify was obtained.

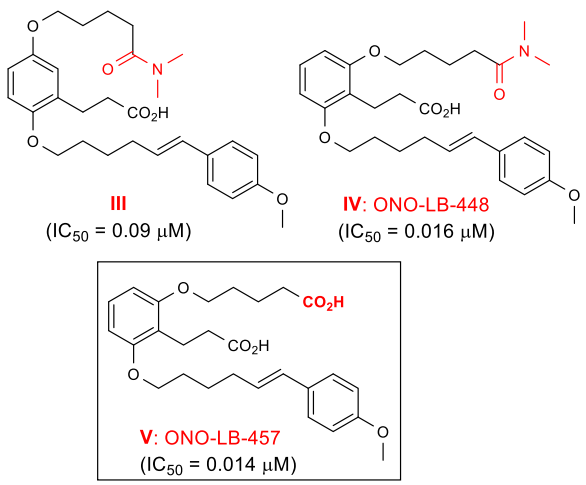
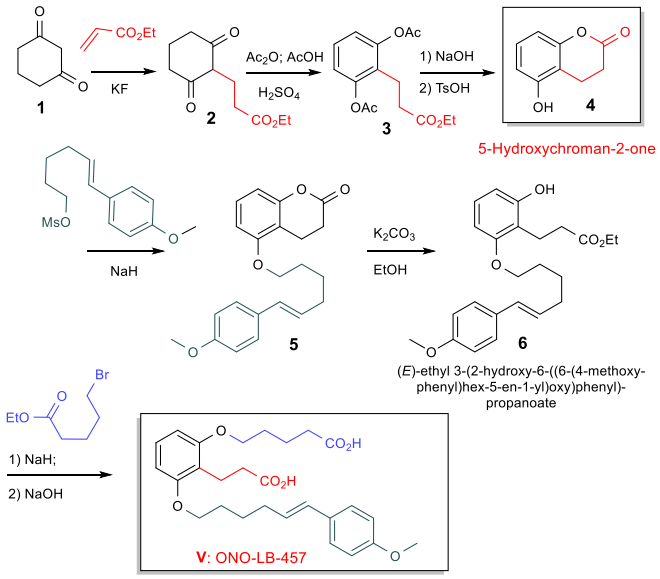
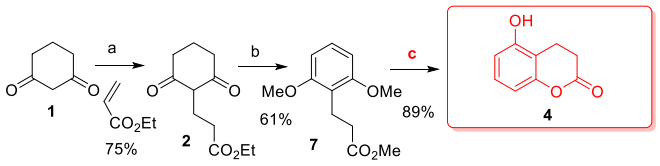


Fig. 4. Structural leukotriene B_4 analogues.



Scheme 1. Previous work: synthesis of compound **V** (ONO-LB-457) reported by Konno's group from 1,3-cyclohexane-dione [20].



Scheme 2. Preparation of chroman-2-one **4** according to the methodology described in the literature by Sharma et al. [28].

Subsequently, the aromatization stage of the cyclohexanedione with a mixture of acid and acetic anhydride [20a], with iodine and methanol [28a] or with copper chloride in a basic medium [27b] leads to the expected substituted benzene with yields lower than 40%, yields based on products purified by column chromatography. It should be noted that in its synthesis Konno et al. they do not describe the yields of their work [20a] or they indicate the yields of the compounds without purification by chromatography [27b].

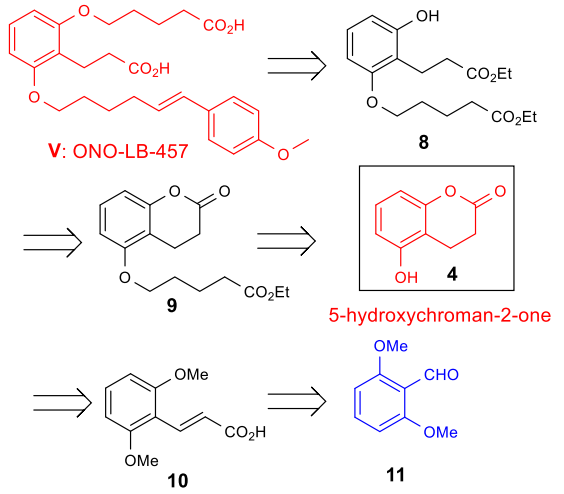
In view of the drawbacks found in these preliminary tests, our objective focused on the preparation of **V**: ONO-LB-457 with an alternative synthesis. The strategy described below was focused primarily on optimizing the preparation of the 5-hydroxychroman-2-one **4**, starting this time from the commercial compound, 2,6-dimethoxy-benzaldehyde (**11**) (see Scheme 3).

The first stage of this synthesis requires the condensation of the aldehyde **11** with the malonic acid by applying the Doebner-modified methodology of the Knoevenagel reaction [29–32].

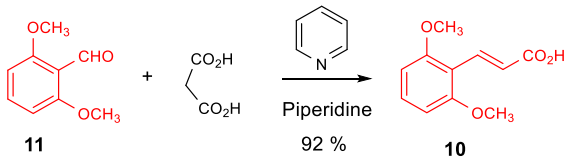
This reaction was conducted in pyridine in presence of catalytic amount of piperidine (Scheme 4).

The 2,6-methoxycinnamic acid (**10**), was recently described in a study carried out by a Chinese team on a traditional herbal of local origin [33].

Catalytic hydrogenation of the double bond of acid **10** was carried out in the presence of palladium, in acetic acid. The 3-(1,3-dimethoxybenzen-2-yl)propanoic acid (**12**) was thus isolated in 82% yield. This reaction was followed by cleavage of the methoxy



Scheme 3. This work: Retrosynthesis of ONO-LB-457 compound prepared from 2,6-dimethoxybenzaldehyde.



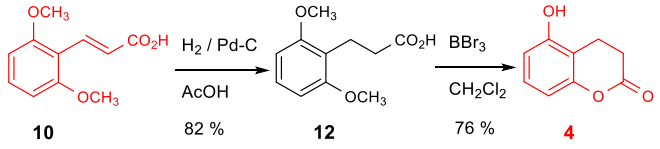
Scheme 4. Preparation of **10**.

groups by the action of boron tribromide, leading to an intramolecular cyclization reaction to form the desired 5-hydroxychroman-2-one **4** with 76% yield (Scheme 5). The overall yield for the preparation of **4** from aldehyde **11** was 57%, much higher than the described methods of which we are aware.

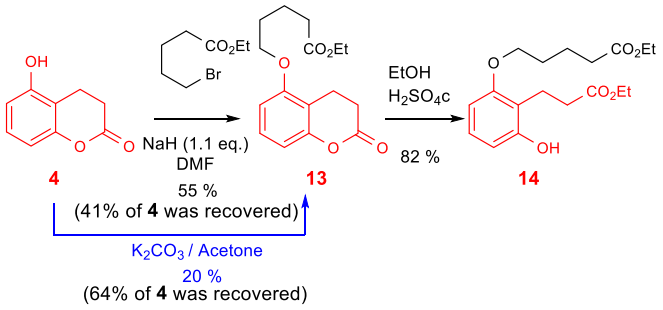
We subsequently followed the best conditions for the preparation of ethyl 5-((2-oxochroman-5-yl)oxy)pentanoate (**13**). A few preliminary tests of the nucleophilic substitution reaction of ethyl 5-bromovalerate with the 5-hydroxychroman-2-one **4** were carried out in the presence of potassium carbonate in refluxing acetone. This proved unsuccessful, with yields below 20%.

The nucleophilic substitution reaction was accomplished, however, preparing the phenoxide with sodium hydride (NaH) in *N*,*N*-dimethylformamide with 55% of yield of the purified product. With both pathways, either potassium carbonate (K_2CO_3) or sodium hydride (NaH) as base, we recovered part of the unreacted starting substrate. In the best case, 41% of the starting material was recovered with sodium hydride, or 64% when carbonate was used (Scheme 6).

An increase in the number of NaH equivalents gave only secondary products, which are due to the presence of the acidic proton at alpha carbonyl position of 5-hydroxychroman-2-one **4**, in addition to the products of unidentified degradations.



Scheme 5. Preparation of 5-hydroxychroman-2-one **4**.



Scheme 6. Synthesis of phenolic diester **14** from 5-hydroxychroman-2-one (**4**).

Despite this disappointing result, we continued our work by preparing the trisubstituted homocycle. Ring opening by an attack at C-2 was not followed by re-cyclization products, as it often is in the monocyclic series. Ring-opened products were therefore isolated. The opening of the lactone **13** carried out in ethanol at reflux in the presence of concentrated sulfuric acid, led to the phenolic diester **14** with 82% of yield (Scheme 6).

To complete the synthesis of **V**, the preparation of the intermediate compound (*E*)-6-(4-methoxyphenyl)hex-5-en-1-yl methanesulfonate (**18**) was carried out. This compound was obtained in three steps from 5-bromovaleric acid (**15**), using the Wittig reaction conditions in the key step of this sequence (Scheme 7).

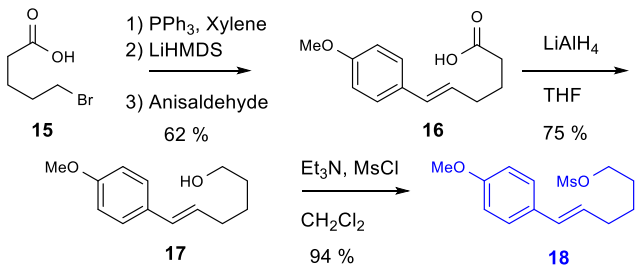
The reaction of 5-bromovaleric acid (**15**) with triphenylphosphine gives phosphonium salt, which subsequently allows the Wittig reaction on anisaldehyde in the presence of LiHMDS [34].

Subsequently, the majority product of the derivative (*E*)-6-(4-methoxyphenyl)hex-5-enoic acid (**16**) was obtained, with a yield of 62%, and the analytical data is in accordance with the work carried out by the group of Maryanoff (Scheme 7). [35, 36].

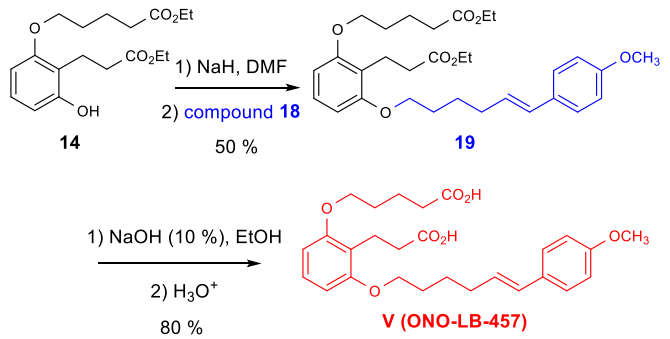
(*E*)-6-(4-Methoxyphenyl)hex-5-en-1-ol (**17**) was prepared from the corresponding carboxylic acid by reduction with lithium aluminum hydride in tetrahydrofuran. While the mesylate **18** was obtained directly from the alcohol, (*E*)-6-(4-methoxyphenyl)hex-5-en-1-ol (**17**) applying classical conditions (Scheme 8). Finally, compound **19** was prepared as indicated in Scheme 8.

The substitution of mesylate (*E*)-6-(4-methoxyphenyl)hex-5-en-1-yl methanesulfonate (**18**), with ethyl 5-(2-(3-ethoxy-3-oxopropyl)-3-hydroxyphenoxy)-pentanoate (**14**) previously prepared, in the presence of sodium hydride afforded **19** with an average yield of 50%.

In this case, 30% of the starting product **14** was recovered, and was used for a new synthesis of compound **19**. The hydrolysis of the ester derivative **19** in a basic solution of 10% NaOH in EtOH afforded the desired product **V** (ONO-LB-457) with 80% yield.



Scheme 7. Synthesis of (*E*)-6-(4-methoxyphenyl)hex-5-en-1-yl methanesulfonate (**18**) from 5-bromovaleric acid (**15**).



Scheme 8. Synthesis of **V** (ONO-LB-457) from ethyl 5-(2-(3-ethoxy-3-oxopropyl)-3-hydroxyphenoxy)pentanoate.

3. Conclusion

The results obtained in the attempts to reproduce the synthetic route used by Konno et al. for the preparation of the ONO-LB-457 compound have led us to apply alternative routes.

Knoevenagel condensation between aldehyde and malonic acid, followed by double reduction and subsequent deprotection and cyclization, have allowed the chroman-2-one **4** to be achieved with an overall yield of 57%. It has also been shown that the Wittig reaction allows the mesylated key intermediate **18** to achieve an overall yield of 44% from 5-bromovaleric acid in three steps.

The preparation of ONO-LB-457, which is a leukotriene B4 receptor antagonist, has been achieved by a convergent synthesis different from that previously described by other authors for the same compound. The number of stages has been reduced and the overall yields turns out to be higher.

4. Experimental

4.1. General experimental

All reagents were purchased from commercial suppliers and were used without further purification. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (60 F254) plates. Compounds were visualized by UV irradiation at 256 or 365 nm. Flash column chromatography was performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm). Melting points (mp [°C]) were taken on samples in open capillary tubes. Infrared spectra of compounds were recorded with a Thermo Scientific Nicolet iS10 instrument. ^{1}H NMR spectra were recorded with a Bruker spectrometer at 400 MHz. Chemical shifts are given in parts per million (ppm) from tetramethylsilane (TMS) as internal standard in $CDCl_3$, and the residual peak of DMSO in [D_6] DMSO. The following abbreviations are used for the ^{1}H NMR spectra multiplicities: br. s: broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, qt: quintuplet, m: multiplet. Coupling constants (J) are reported in Hertz [Hz]. High Resolution Mass Spectrometry data (HRMS) were adquired using a LC/MSD-TOF analyser in methanol or acetonitrile.

4.2. Synthesis of the 3,4-dihydro-5-hydroxy-chromen-2-one **4**

4.2.1. (E)-3-(2,6-Dimethoxyphenyl)acrylic acid (**10**)

To a solution of 2,5-dimethoxy-benzaldehyde (3.4 g, 20.0 mmol) in 15 mL of pyridine, piperidine (0.4 mL) and the malonic acid (4.26 g, 41.0 mmol) was added. The reaction mixture was stirred at 85 °C for 1 h, and 3 h at 110 °C. The solid residue was solubilized in 160 mL of water. The solution was slowly acidified by addition of aqueous HCl to pH = 2 until crystal appeared. The crystal was filtered, washed with water and dried. Yield: 92%; mp: 152–154 °C [literature: mp: 154–156 °C **[28]**; mp: 151–153 °C **[29]**; IR (cm-1): 3269 (OH), 1702 (C=O), 1091 (C–O); ^{1}H NMR ($CDCl_3$ + D_2O) δ (ppm), 8.10 (d, J = 16.1 Hz, 1H), 7.13 (t, 1H, J = 8.3 Hz), 6.80 (d, J = 16.1 Hz, 1H), 6.60 (d, 2H, J = 8.3 Hz), 3.85 (s, 6H); HRM: ESI(−)(M − 1) cald for $C_{11}H_{11}O_4$, 207.0657, found, 207.0660 [29–32].

4.2.2. 3-(2,6-Dimethoxyphenyl)propanoic acid (**12**)

To a solution of the corresponding previously obtained acid **10** (4.26 g, 20.4 mmol) in acetic acid (70 mL) was added 10% Pd/C (2.12 g). The reaction mixture was stirred under hydrogen atmosphere until the complete consumption of the starting material (4 h). The mixture was filtered through Celite and evaporation of the solvent in vacuo provided a crude residue, which was purified by chromatography on silica gel using ($MeOH/CH_2Cl_2$, 6/94) to afford compound **12** as a white solid. Yield: 82%; mp: 109–111 °C; IR (cm^{-1}): 3772-2556 (OH), 1696 (C=O); ^{1}H NMR (DMSO + D_2O) δ (ppm),7.13 (t, 1H, J = 8.3 Hz), 6.60 (d, 2H, J = 8.3 Hz), 3.75 (s, 6H), 2.79 (t, 2H, J = 8.0 Hz), 2.27 (t, 2H, J = 8.0 Hz); HRM: ESI(−)(M − 1) cald for $C_{11}H_{13}O_4$, 209.0814, found, 209.0821.

4.2.3. 3,4-Dihydro-5-hydroxychromen-2-one (**4**)

Under nitrogen atmosphere, boron tribromide (2.24 mL; 23.75 mmol, 2.5 eq.) was slowly added to a solution of the corresponding acid **12** (2 g, 9.5 mmol) in (150 mL) anhydrous CH_2Cl_2. The reaction mixture was stirred at room temperature for 1 h and poured onto iced water. The aqueous layer was extracted three times with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel using a CH_2Cl_2 to afford the desired product **4** as a white solid. Yield 76%; mp: 170–172 °C; IR (cm^{-1}): 3261 (OH), 1723 (C=O); ^{1}H NMR ($CDCl_3$ + D_2O) δ (ppm),7.10 (t, 1H, J = 8.2 Hz), 6.67 (d, 1H, J = 8.2 Hz), 6.57 (d, 1H, J = 8.2), 3.00 (t, 2H, J = 7.5 Hz), 2.78 (t, 2H, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$ + D_2O) δ (ppm), 17.6, 29.0, 107.1, 109.4, 129.5, 152.6, 157.1, 171.2; HRM: ESI(+)(M+1) cald for $C_9H_9O_3$, 165.0552, found, 165.0559.

4.3. Synthesis of phenolic diester **14**

4.3.1. Ethyl 5-(3,4-dihydro-2-oxo-2H-chromen-5-yloxy)pentanoate (**13**)

Sodium hydride (80% w/w, 0.11 g, 3.67 mmol) was added portion wise to a stirred solution of 5-hydroxychroman-2-one (**4**) (0.55 g, 3.3 mmol) in dry DMF (10 mL). The solution was stirred under nitrogen atmosphere at room temperature for 20 min and a solution of ethyl 5-bromovalerate (0.64 mL, 4.0 mmol) in dry DMF (1 mL) was added dropwise. The resulting mixture was stirred for 1 h at 60 °C, then poured onto iced water and the solution was slowly acidified by addition of aqueous (1 N) HCl. The aqueous layer was extracted three times with AcOEt, and the combined organic layers were dried over $MgSO_4$, filtered, checked with TLC plate and concentrated in vacuo. The resulting residue was purified by silica gel chromatography using a mixture (AcOEt/EP, 30/70) to separate the starting material (41%) of the desired compound **13** as a white solid. Yield 55%; mp: 57–59 °C; IR (Nujol) (cm^{-1}): 1765 and 1721 (C=O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.17 (t, 1H, J = 8.2 Hz), 6.68 (d, 1H, J = 8.2 Hz), 6.63 (d, 1H, J = 8.2 Hz), 4.14 (q, 2H, J = 7.2 Hz), 4.00 (m, 2H), 2.98 (t, 2H, J = 7.6 Hz), 2.75 (t, 2H, J = 7.6 Hz), 2.38 (m, 2H), 1.85 (m, 4H), 1.26 (t, 3H, J = 7.2 Hz); HRM: ESI(+)(M+1) cald for $C_{16}H_{21}O_5$, 293.1389, found, 293.1392.

4.3.2. Ethyl 5-[2(3-ethoxy-3-oxopropyl)-3-hydroxyphenoxy] pentanoate (**14**)

To a solution of ester **13** (0.542 g, 1.86 mmol) in ethanol (15 mL), 4 mL of sulfuric acid was slowly added while stirring. The reaction mixture was stirred at 60 °C for 4 h, and then partitioned between AcOEt and water. The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The solid residue was purified by chromatography on silica gel using (Ether/CH_2Cl_2, 1/99) to afford the desired product **14** as a solid. Yield 82%; mp: 67–68 °C; IR (cm^{-1}): 3376 (OH), 1731 and 1713 (C=O); ^1H NMR ($CDCl_3 + D_2O$) δ (ppm), 7.06 (t, 1H, $J = 8.1$ Hz), (d, 1H, $J = 8.1$ Hz), 6.42 (d, 1H, $J = 8.1$ Hz), 4.14 (m, 4H), 3.95 (m, 2H), 2.90 (t, 2H, $J = 6.6$ Hz), 2.70 (t, 2H, $J = 6.6$ Hz), 2.39 (m, 2H), 1.83 (m, 4H), 1.25 (m, 6H); HRM: ESI(+)(M+1) cald for $C_{18}H_{27}O_6$, 339.1808, found, 339.1807.

4.4. Synthesis of (E)-6-(4-methoxyphenyl)hex-5-en-1-yl methanesulfonate (**18**)

4.4.1. (E)-6-(4-Methoxyphenyl)hex-5-enoic acid (**16**)

The phosphonium salt, (4-carboxybutyl)triphenyl phosphonium bromide was previously prepared from 5-bromovaleric acid (**15**) and triphenylphosphine according to the following procedure: In a 250 mL flask equipped with a refrigerant containing 10.0 g of 5-bromovaleric acid **15** (1 eq, 55.2 mmol), 16.0 g of triphenylphosphine (1.1 eq., 61.0 mmol) and 150 mL of xylene were added. The mixture was heated at reflux for 2 h with stirring. After cooling the mixture to room temperature, the white precipitate formed was filtered on sintered glass and washed with acetone. After drying, 15.92 g of (4-carboxybutyl)triphenyl-phosphonium bromide were recovered as a white solid with 65% yield.

Thereafter, to a stirred solution of hexamethyldisilazane (12.23 mL, 58.0 mmol) in anhydrous THF (60 mL) under nitrogen, *n*-butyllithium (1.6 in hexane, 33.75 mL, 54 mmol) was added at 0 °C. After 30 min at 0 °C, a solution of (4-carboxybutyl)triphenylphosphonium bromide (9 g, 20.31 mmol) in anhydrous THF (100 mL) was added *via* cannula slowly. The solution was vigorously stirred for 30 min, and a solution of anisaldehyde (3 mL, 24.72 mmol) was added. The resulting mixture was stirred for 2 h and subsequently quenched with water (160 mL). The homogeneous solution was acidified to p$H = 2$ with an aqueous solution of sulfuric acid. The aqueous layer was extracted with AcOEt, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel using a mixture (AcOEt/EP/AcOH, 90/9/1) to afford the desired product **16** as a solid. Yield 62%; mp: = 76–78 °C; IR (cm^{-1}): 3730-2500 (OH), 1709 (C=O), 1611 (C=C); ^1H NMR ($CDCl_3 + D_2O$) δ (ppm), 7.26 (d, 2H, $J = 8.7$ Hz), 6.83 (d, 2H, $J = 8.7$ Hz), 6.35 (d, 1H, $J = 15.7$ Hz), 6.10–5.96 (m, 1H), 3.08 (s, 3H), 2.41 (t, 2H, $J = 7.4$ Hz), 2.26 (q, 2H, $J = 7.4$ Hz), 1.81 (q, 2H, $J = 7.4$ Hz).

4.4.2. (E)-6(4-methoxyphenyl)-5-hexen-1-ol (**17**)

Lithium aluminum hydride (2 g, 52.7 mmol) in anhydrous THF (100 mL) was added portion wise at 0 °C to a stirred solution of acid **16** (2.79 g, 12.68 mmol) in 100 mL of THF. The solution was stirred under nitrogen atmosphere at 25 °C for 4 h and poured onto iced water. Solution of KOH (3 M, 2 mL) and 6.75 mL water were added and the reaction mixture was stirred for 1 h. The resulting suspension was filtered. The filtrate was dried over $MgSO_4$; the solvent was removed in vacuo. The residue was purified by chromatography on silica gel using a mixture (AcOEt/EP, 50/50) to afford the desired product **17** as a white solid. Yield 75%; mp = 57–60 °C; IR (cm^{-1}): 3614-3102 (OH), 1606 (C=C); ^1H NMR ($CDCl_3 + D_2O$) δ (ppm), 7.26 (d, 2H, $J = 8.7$ Hz), 6.83 (d, 2H, $J = 8.7$ Hz), 6.34 (d, 1H, $J = 15.7$ Hz), 6.13–6.00 (m, 1H), 3.79 (s, 3H), 3.68 (t, 2H, $J = 6.4$ Hz), 2.22 (q, 2H, $J = 7.1$ Hz), 1.69–1.46 (m, 4H); HRM: ESI(+)(M+1) cald for $C_{13}H_{18}O_2$, 206.1307, found, 206.1310.

4.4.3. (E)-6(4-methoxyphenyl)-5-hexenyl methane sulfonate (**18**)

At 0 °C, mesyl chloride (0.8 mL, 10.33 mmol) was added dropwise to a stirred solution of the alcohol **17** (1.66 g, 8.05 mmol) in CH_2Cl_2 (60 mL) and (4.7 mL). The solution was stirred under nitrogen atmosphere at 0 °C for 1 h and was hydrolyzed with water. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, the solvent was evaporated, and the crude product was purified by chromatography on silica gel using a mixture (AcOEt/EP, 46/54) to afford the desired product **18** as crystallizing oil. Yield 94%; mp = 32–33 °C; IR (cm^{-1}): 2983 (CH), 1605 (C=C); ^1H NMR ($CDCl_3$) δ (ppm), 7.27 (d, 2H, $J = 8.7$ Hz), 6.83 (d, 2H, $J = 8.7$ Hz), 6.35 (d, 1H, $J = 15.8$ Hz), 6.09–5.96 (m, 1H), 4.25 (t, 2H, $J = 6.5$ Hz), 3.80 (s, 3H), 3.00 (s, 3H), 2.25 (q, 2H, $J = 7.3$ Hz), 1.81 (q, 2H, $J = 7.3$ Hz), 1.59 (q, 2H, J = 7.5 Hz); HRM: ESI(+)(M+1) cald for $C_{14}H_{20}O_4S$, 284.1082, found, 284.1087.

4.5. Synthesis of **V** (ONO-LB-457) from phenolic diester **14**

4.5.1. Ethyl 5-(2-(3-ethoxy-3-oxopropyl)-3-{[(E)-6(4-methoxyphenyl)-5-hexenyl]oxy}-phenoxy)penta neate (**19**)

Sodium hydride (0.173 g, 3.23 mmol) was added portionwise to a stirred solution of phenol **14** (0.79 g, 2.43 mmol) in dry DMF (16 mL). The solution was stirred under nitrogen atmosphere at room temperature for 15 min and a solution of the mesylate **18** (0.55 g, 1.94 mmol) in dry DMF (4 mL) was added dropwise. The resulting mixture was stirred for 2 h at 60 °C, then poured onto iced water and the solution was slowly acidified by addition of aqueous (1 N) HCl. The aqueous layer was extracted three times with AcOEt, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel using a (CH_2Cl_2) to afford the desired product **19** as a colorless oil. Yield 50%; IR (cm^{-1}): 1738 (C=O), 1650 (C=C); ^1H NMR ($CDCl_3$) δ (ppm), 7.27 (d, 2H, $J = 8.8$ Hz), 7.07 (t, 1H, $J = 8.1$ Hz), 6.82 (d, 2H, $J = 8.8$ Hz), 6.48 (m, 2H), 6.35 (d, 1H, $J = 15.4$ Hz), 6.14–6.01 (m, 1H), 4.09 (m, 4H), 3.96 (m, 4H), 3.79 (s, 3H), 3.02 (t, 2H, $J = 8.1$ Hz), 2.49 (t, 2H, $J = 8.1$ Hz), 2.38 (m, 2H), 2.25 (q, 2H, $J = 7.3$ Hz), 1.83 (m, 6H), 1.66 (q, 2H, $J = 7.4$ Hz), 1.23 (m, 6H); HRM: ESI(+)(M+1) cald for $C_{31}H_{43}O_7$, 527.3009, found, 527.3011.

4.5.2. 5-(2-(2-Carboxyethyl)-4-meyhoxy-3-{[(E)-6-(4-methoxyphenyl)-5-hexenyl]-oxy}-phenoxy)-pentanoic acid (**V**) (**ONO-LB-457**)

To a solution of ester **19** (0.62 g, 1.17 mmol) in ethanol (40 mL), 10% the potassium hydroxide (0.7 g, 17.57 mmol/in 14 mL water) was slowly added. The reaction mixture was stirred for 24 h min at room temperature and was hydrolyzed with water. The aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The solid residue was purified by chromatography on silica gel using a mixture (MeOH/CH_2Cl_2, 10/90) to afford the desired product **V** as white crystals. Yield 80%; mp = 146–148 °C; IR (cm^{-1}): 3640-3000 (OH), 1712 (C=O). ^1H NMR ($CDCl_3$+ D_2O) δ (ppm), 7.24 (d, 2H, $J = 8.8$ Hz), 7.00 (t, 1H, $J = 8.1$ Hz), 6.80 (d, 2H, $J = 8.8$ Hz), 6.43 (d, 1H, $J = 8.1$ Hz), 6.37 (d, 1H, J = 8.1 Hz), 6.30 (d, 1H, $J = 15.4$ Hz), 6.02 (m, 1H), 3.94–3.78 (m, 4H), 3.76 (s, 3H), 2.97 (m, 2H), 2.45 (m, 2H), 2.33 (m, 2H), 2.19 (q, 2H, $J = 7.3$ Hz), 1.90–1.63 (m, 6H), 1.56 (m, 2H); SM (IC/NH_3): $m/z = 470$ (M); 471 (M+1).

Declaration of competing interest

The authors declare that they have no known competing

financial interest or potential relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This work was supported by ICOA (*Institut de Chimie Organique et Analytique*), University of Orleans (France).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131740.

References

[1] P. Borgeat, B. Samuelsson, Proc. Natl. Acad. Sci. U.S.A. 76 (1979) 3213–3217.
[2] R.J. Smith, S.S. Iden, B.J. Bowman, Inflammation 8 (1984) 365–384.
[3] M.J.H. Smith, A.W. Ford-Hutchinson, M.A. Bray, J. Pharm. Pharmacol. 32 (1980) 517–518.
[4] N.D. Kim, A.D. Luster, Sci. World J. 7 (2007) 1307–1328.
[5] A. Sala, G. Folco, R.C. Murphy, Pharmacol. Rep. 62 (2010) 503–510.
[6] G. Folco, R.C. Murphy, Pharmacol. Rev. 58 (2006) 375–388.
[7] D.M. Tobin, F.J. Roca, S.F. Oh, R. McFarland, T.W. Vickery, J.P. Ray, D.C. Ko, Y. Zou, N.D. Bang, T.T. Chau, J.C. Vary, T.R. Hawn, S.J. Dunstan, J.J. Farrar, G.E. Thwaites, M.C. King, C.N. Serhan, L. Ramakrishnan, Cell 148 (2012) 434–446.
[8] C.N. Serhan, Annu. Rev. Immunol. 25 (2007) 101–137.
[9] J.M. Dayer, S. Demczuk, Springer Semin. Immunopathol. 7 (1984) 387–413.
[10] B. Samuelsson, S. Hammarström, R.C. Murphy, P. Borgeat, Allergy 35 (1980) 375–381.
[11] B. Samuelsson, Angew. Chem. Int. Ed. 21 (1982) 902–910.
[12] P. Sirois, S. Roy, P. Borgeat, S. Picard, P. Vallerand, Prostag. Leukotr. Med. 8 (1982) 157–170.
[13] A. Bafica, C.A. Scanga, C. Serhan, F. Machado, S. White, A. Sher, J. Aliberti, J. Clin. Invest. 115 (2005) 1601–1606.
[14] K.A. Lundeen, B. Sun, L. Karlsson, A.M. Fourie, J. Immunol. 177 (2006) 3439–3447.
[15] T.S. Hallstrand, W.R. Henderson Jr., Curr. Opin. Allergy Clin. Immunol. 10 (2010) 60–66.
[16] P. Montuschi, Pharmaceuticals 3 (2010) 1792–1811.
[17] P. Montuschi, A. Sala, S.-E. Dahlén, G. Folco, Drug Discov. Today 12 (2007) 404–412.
[18] S.E. Dahlen, Eur. J. Pharmacol. 533 (2006) 40–56.
[19] R.A. Goodnow Jr., A. Hicks, A. Sidduri, A. Kowalczyk, R. Dominique, Q. Qiao, J.P. Lou, P. Gillespie, N. Fotouhi, J. Tilley, N. Cohen, S. Choudhry, G. Cavallo, S.A. Tannu, J.D. Ventre, D. Lavelle, N.S. Tare, H. Oh, M. Lamb, G. Kurylko, R. Hamid, M.B. Wright, A. Pamidimukkala, T. Egan, U. Gubler, A.F. Hoffman, X. Wei, Y.L. Li, J. O'Neil, R. Marcano, K. Pozzani, T. Molinaro, J. Santiago, L. Singer, M. Hargaden, D. Moore, A.R. Catala, L.C.F. Chao, G. Hermann, R. Venkat, H. Mancebo, L.M. Renzetti, J. Med. Chem. 53 (2010) 3502–3516.
[20] a) M. Konno, T. Nakae, N. Hamanaka, Eur. Pat. Appl. 115 (1991) 28892j, 0405116B1, Ono Pharmaceutical Co., Ltd. (January 02, 1991); Chem. Abstr.;
b) M. Konno, T. Nakae, S. Sakuyama, Y. Odagaki, H. Nakai, N. Hamanaka, Bioorg. Med. Chem. 5 (1997) 1649–1674.
[21] M. Konno, S. Sakuyama, T. Nakae, N. Hamanaka, T. Miyamoto, A. Kawasaki, Leukotriene Res. 21A (1991) 411–414.
[22] S.W. Djuric, P.W. Collins, P.H. Jones, R.L. Shone, B.S. Tsai, D.J. Fretland, G.M. Butchko, D. Villani-Price, R.H. Keith, J.M. Zemaitis, L. Metcalf, R.F. Bauer, J. Med. Chem. 32 (1989) 1145–1147.
[23] A.H. Lin, J. Morris, D.G. Wishka, R.R. Gorman, Ann. N. Y. Acad. Sci. 524 (1988) 196–200.
[24] K. Kashikawa, N. Tateishi, T. Maruyama, R. Seo, M. Toda, T. Miyamoto, Prostaglandins 44 (1992) 261–275.
[25] B.S. Tsai, R.H. Keith, D. Villani-Price, J.F. Kachur, D.C. Yang, S.W. Djuric, S. Yu, J. Pharmacol. Exp. Therapeut. 268 (1994) 1499–1505.
[26] F.-C. Huang, W.-K. Chan, J.D. Warus, M.M. Morrissette, K.J. Moriarty, M.N. Chang, J.J. Travis, L.S. Mitchell, G.W. Nuss, C.A. Sutherland, J. Med. Chem. 35 (1992) 4253–4255.
[27] (a) M. Konno, T. Nakae, S. Sakuyama, K. Nishizaki, Y. Odagaki, H. Nakai, N. Hamanaka, Bioorg. Med. Chem. 5 (1997) 1621–1647;
(b) M. Konno, T. Nakae, S. Sakuyama, K. Imaki, H. Nakai, N. Hamanaka, Synlett (1997) 1472–1474.
[28] (a) D. Sharma, C.B. Reddy, A.K. Shil, R.P. Saroach, P. Das, Mol. Divers. 17 (2013) 651–659;
(b) D. Sharma, A.K. Shil, B. Singh, P. Das, Synlett 23 (2012) 1199–1204;
(c) 21. P. Das, D. Sharma, B. Singh (2011). WO/2011/117881. (d) D. Sharma, Bandna, C.B. Reddy, S. Kumar, A.K. Shil, N.R. Guha, P. Das, RSC Adv. 3 (2013) 10335–10340;
(e) J.M. Kim, K.Y. Lee, J.N. Kim, Bull. Kor. Chem. Soc. 24 (2003) 1057–1058, https://doi.org/10.5012/bkcs.2003.24.8.1057;
(f) L. Zuo, S. Yao, W. Wang, W. Duan, Tetrahedron Lett. 49 (2008) 4054–4056.
D.L. Terrian, T. Mohammad, H. Morrison, J. Org. Chem. 60 (1995) 1981-1984.
[29] H.A. Shah, R.C. Shah, J. Chem. Soc. (1938) 1832–1833.
[30] M. Tanaka, O. Oota, H. Hiramatsu, K. Fujiwara, Bull. Chem. Soc. Jpn. 61 (1988) 2473–2479.
[31] O.B. Berryman, A.C. Sather, A. Lledó, J. Rebek Jr., Angew Chem. Int. Ed. Engl. 50 (2011) 9400–9403.
[32] Y. Bai, X. He, Y. Bai, Y. Sun, Z. Zhao, X. Chen, B. Li, J. Xie, Y. Li, P. Jia, X. Meng, Y. Zhao, Y. Ding, C. Xiao, S. Wang, J. Yu, S. Liao, Y. Zhang, Z. Zhu, Q. Zhang, Y. Zhao, F. Qin, Y. Zhang, X. Wei, M. Zeng, J. Liang, Y. Cuan, G. Shan, T.-P. Fan, B. Wu, X. Zheng, Eur. J. Med. Chem. 183 (2019) 111650–111677.
[33] D.M. Gapinski, B.E. Mallet, L.L. Froelich, W.T. Jackson, J. Med. Chem. 33 (1990) 2798–2807.
[34] B.E. Maryanoff, B.A. Duhl-Emswiler, Tetrahedron Lett. 22 (1981) 4185–4188.
[35] B.E. Maryanoff, A.B. Reitz, B.A. Duhl-Emswiler, Tetrahedron Lett. 24 (1983) 2477–2480.
[36] B.E. Maryanoff, A.B. Reitz, B.A. Duhl-Emswiler, J. Am. Chem. Soc. 107 (1985) 217–226.