



# Ferrocene derivatives of liquid chiral molecules allow assignment of absolute configuration by X-ray crystallography



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## ARTICLE INFO

### Article history:

Received 15 August 2017

Revised 21 August 2017

Accepted 1 September 2017

Available online 6 October 2017

Dedicated to the memory of Dr. Howard Flack

## ABSTRACT

The present study investigates a synthetically simple ferrocene derivatization of natural products and active pharmaceutical ingredients. Seven new crystal structures are analyzed together with 16 structures of ferrocene derivatives reported previously. In all cases, the unambiguous determination of the absolute structure was established from anomalous dispersion using the methods of Flack and Parsons. A comparison with other derivatization approaches shows the advantage of the described ferrocene derivatization for establishing the absolute configuration of novel compounds.

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## 1. Introduction

Chirality plays a central role in biological recognition processes. Therefore, the vast majority of molecules addressing biological receptors such as natural products, active pharmaceutical ingredients and fragrances are chiral. Asymmetric syntheses and enantioselective total syntheses have seen recent major advances. Unfortunately, we are facing deficits in the analysis of unknown compounds as witnessed by the considerable number of wrongly assigned natural products in the literature.<sup>1,2</sup> As a consequence, the correction of structural assignments for natural products is a common outcome of total syntheses. Although these efforts correct wrongly assigned structures in the literature, it is a very costly way to do so. New methods for better and easier determination of the absolute configuration are still necessary. Currently a general approach for the absolute structure determination does not exist<sup>3,4</sup> and different methods are available including NMR,<sup>5–7</sup> chiroptical spectroscopic methods<sup>8</sup> and X-ray diffraction.<sup>9,10</sup> When crystals of a molecule of interest are obtained, single-crystal X-ray crystallography is the method of choice for structure elucidation.<sup>9,10</sup> It gives access to the three dimensional structure of a molecule and, with the method introduced by Flack, also allows the determination of

the absolute structure of a crystal on a routine basis.<sup>11–14</sup> This in turn allows the assignment of the absolute configuration of the chiral molecules contained in the crystal structure. Hoof et al.<sup>15</sup> and Parsons et al.<sup>16</sup> have further optimized this approach which even allows the absolute structure determination of molecules containing only light atoms.<sup>17</sup>

With advances in primary beam intensity, computational power and X-ray detectors, the measurement as well as the refinement have become fast processes, which make crystallography a rapid technique to determine previously unknown molecular structures. However, the route from a pure compound to a suitable single crystal is often tedious and the bottle neck of the process.<sup>10</sup> Samples which are liquid at room temperature represent a particular challenge. Although crystallization under cryogenic conditions is possible, it requires specialized equipment and takes considerable effort.<sup>18</sup> Even solid samples can require crystallization to give a single crystal of good quality.<sup>19</sup> It is therefore not surprising that the discussion about crystal size and quality can lead to incomprehension between crystallographer and synthetic chemist. In some cases special equipment or sophisticated methods can help. Tiny crystals with dimensions below  $0.1 \times 0.1 \times 0.1 \text{ mm}^3$  can nowadays be measured on modern in-house diffractometers and more primary beam intensity is available at modern synchrotron X-ray diffraction beamlines. Fujita et al. presented the crystalline sponge method, a supramolecular approach, which is based on soaking small molecules into MOF crystals.<sup>20</sup> Its procedure has been critically assessed,<sup>21</sup> further optimized<sup>22</sup> and successfully applied for

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assigning the absolute configuration of natural products.<sup>23,24</sup> Nevertheless, establishing the absolute configuration of liquid or non-crystalline compounds remains a challenge frequently encountered in the synthetic laboratory. Historically organic chemists solve this problem by derivatization. Before the arrival of powerful spectroscopic methods, crystallization and determination of melting points were of central importance as purification and analytical methods, respectively. From the late 19<sup>th</sup> century, alcohols were converted into the corresponding nitrobenzoates (4-NO<sub>2</sub> or 3,5-(NO<sub>2</sub>)<sub>2</sub> benzoates), and aldehydes and ketones into the corresponding 3,5-(NO<sub>2</sub>)<sub>2</sub>-phenyl hydrazones<sup>25,26</sup> which are characterized by high crystallinity and sharp melting points. Comparison of the obtained melting points allowed the structural identity of products to be proved. Milestones such as Fischer's ground breaking work on sugars and the asymmetric carbon atom itself were based on chemical derivatization.<sup>27,28</sup> The conversion of different sugars into their corresponding osazones<sup>29</sup> (Scheme 1a), which have sharp melting points and stable optical rotations enabled Fischer's fundamental work with which the concept of the chiral carbon atom was introduced into sugar chemistry.<sup>30</sup> The characterization and the first industrial synthesis<sup>31</sup> of vitamin A involved esterification into the corresponding anthraquinone ester **4**<sup>32</sup> for the purpose of recrystallization (Scheme 1b).<sup>33</sup> After purification at this stage, saponification liberates the desired vitamin A in its pure, high melting form.<sup>34</sup>

Of those important derivatization techniques,<sup>35</sup> only the nitrobenzoate derivatization remained and is still routinely used to facilitate the crystallization of difficult samples.<sup>36</sup> Unfortunately, this auxiliary does not introduce a heavy atom or a stereogenic reference center, which would help assigning the absolute configuration by means of X-ray crystallography.

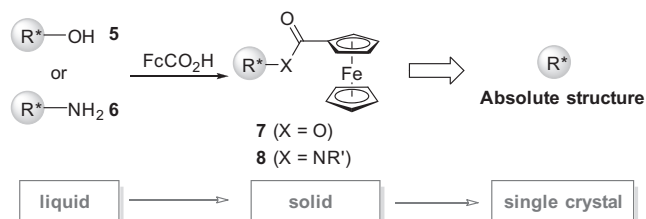
We have identified ferrocene derivatization as a simple and efficient technique for obtaining single crystals. We have found it very useful for establishing the absolute configuration and will start by introducing the rationale behind this idea.

## 2. Concept

With the aim of establishing the absolute configuration of a scalable, liquid sample we searched for an operationally simple way to solve this problem. We sought to render oily organic substrates crystalline by covalently linking them to an organometallic compound with high melting point and good crystallinity. For this purpose ferrocene carboxylic acid seems to be the ideal candidate as it combines several attractive properties:

- Highly crystalline
- Contains a heavy atom for increased diffraction intensity
- Intense anomalous scattering effect allowing for the determination of the absolute structure
- Chemically and thermally stable
- Characteristic orange color
- High sensitivity to electrospray mass spectrometry<sup>37–39</sup>
- Relatively inexpensive or easily synthesized from ferrocene<sup>40</sup>

Based on seminal work by Shibata et al. (vide infra),<sup>41–43</sup> we identified ferrocene carboxylic acid as an ideal auxiliary that could be easily reacted under mild conditions with liquid chiral molecules containing either an alcohol and/or amine functionality (Scheme 2). Either one of these two functional groups is found in most natural products, active pharmaceutical ingredients and in many synthetic intermediates. Therefore, we reasoned that this method should be broadly applicable.



**Scheme 2.** Concept of ferrocene derivatization to transfer liquid, chiral substrates into crystalline solids.

Herein, we will (a) analyze the synthetic scope; (b) discuss the capacities of the method to increase the melting point and yield high quality crystallographic data suitable for unequivocal assignment of the absolute configuration; and (c) comment on its limitations.

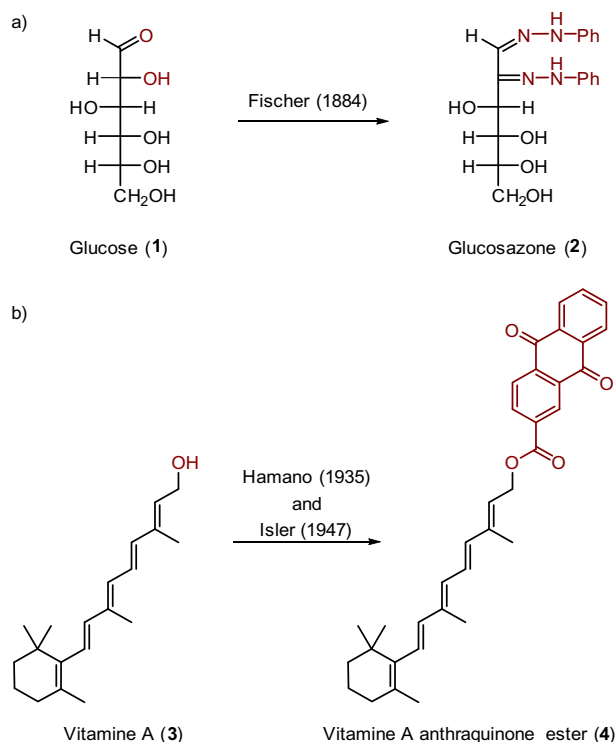
## 3. Results and discussion

### 3.1. Synthetic part

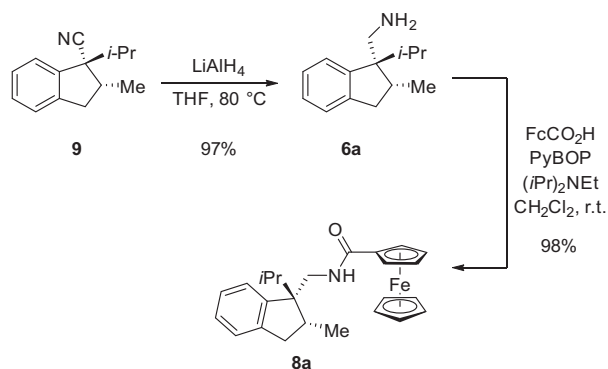
#### 3.1.1. Initial proof of concept

With the above detailed considerations in mind, we set out to test our idea for the first time on indane **6a** (Scheme 3). The correct analysis of its precursor **9** was a center piece to our report on catalytic asymmetric C(sp<sup>3</sup>)-H activation and allowed us to resolve a contradiction between a previous assignment of the absolute configuration and a DFT study.<sup>44</sup> The liquid nitrile **9** was reduced to the liquid amine **6a**, which was finally converted into the solid ferrocenyl amide **8a** by reaction with commercially available ferrocene carboxylic acid. The large (0.60 × 0.48 × 0.34 mm) single crystal obtained gave excellent diffraction data and allowed us to establish the (R,R)-configuration of indane **8a** with high certainty (Flack *x* = 0.006(12)). The corresponding amide derived from 3-bromo benzoic acid remained a liquid and did not allow for crystallographic analysis.<sup>45</sup>

Encouraged by our first example which enabled facile crystallization and resulted in high quality X-ray diffraction data,



**Scheme 1.** Prominent historical examples of derivatizations which improve crystallinity.



**Scheme 3.** Ferrocene derivatization and crystallization of a chiral indane.<sup>44</sup>

the ferrocene derivatization was applied in the total synthesis of aeruginosins.<sup>46,47</sup> The preparation of the octahydroindole core of these molecules involved a nucleophilic substitution step on dibromocyclohexenol **10** to give intermediate **13** (Scheme 4). Although this reaction had been reported previously to proceed with high *cis*-selectivity with sodium azide as the nucleophile,<sup>48</sup> the nucleophilic substitution with an aliphatic amine followed by C(sp<sup>3</sup>)–H activation led to an aeruginosin fragment with a *trans*-configuration. To clarify the outcome of the substitution step, compounds **11** and **12** were prepared. Structural elucidation by NOE NMR would have been particular challenging and so ferrocene derivatization was applied. After deprotection of the alcohol, Steglich esterification with ferrocene carboxylic acid gave **7a** and **7b** as orange solids. Crystals suitable for X-ray crystallography were obtained in the first recrystallization attempt. The crystal structures of **7a** and **7b** allowed us to establish the stereodivergent behavior for the nucleophilic substitution of **10** with different nucleophiles.

### 3.1.2. New ferrocenyl ester and amides

After the success of these two initial applications, we investigated the scope of the ferrocene derivatization by applying it to other chiral or liquid molecules, with a focus on natural products (Scheme 5). Ferrocenyl esters and amides were prepared via ferrocenoyl chloride (method A) or using the activating agent PyBOP (method B). Both protocols were operationally simple and without any optimization, the desired products were obtained in moderate to high yield. The oily monoterpene

alcohols, nerol **5c** and geraniol **5d**, were converted into the corresponding ferrocene carboxylates **7c** and **7d**. The reaction can be easily carried out on a small scale (65  $\mu$ mol scale for **7d**).<sup>49</sup> The characteristic orange color is a particular advantage during chromatographic purification of small amounts because it facilitates product detection. Eugenol, a phenolic fragrance molecule found in cloves, was converted efficiently into the corresponding ferrocene carboxylate **7e**. Recovery of the natural product from ferrocene carboxylates **7** is possible. After saponification of **7e** using lithium hydroxide, we isolated pure eugenol **5e** in 75% yield.<sup>49</sup> The ferrocenyl esters of the secondary alcohols cholesterol **5f**<sup>50,51</sup> and cholestanol **5g**<sup>52</sup> were prepared through reaction with ferrocenoyl chloride at room temperature. Esters of more hindered secondary alcohols, such as testosterone<sup>50</sup> or menthol,<sup>53</sup> could not be obtained at room temperature. Moreover, the esterification of tertiary alcohols was unsuccessful, e.g., (*R*)-linalool **5h** did not react at all. In the literature, the only ferrocene carboxylate issued from a tertiary alcohol was obtained by refluxing ferrocenoyl chloride in *tert*-butanol.<sup>54</sup> These results show that esterification of sterically hindered alcohols is a limitation of our current synthetic strategy. Additionally, it should be mentioned that a small number of ferrocene derivatives remained liquid.

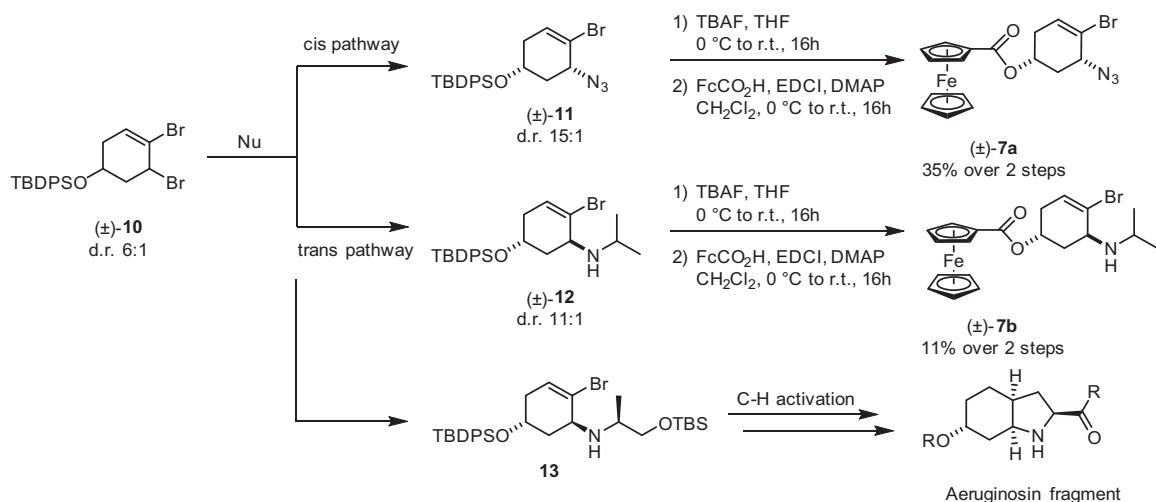
The liquid thiophene building block **6b** was converted into the solid amide **8b** by reacting with ferrocene carboxylic acid. As expected, the secondary amine ephedrine reacted selectively at the nitrogen atom in the presence of a free hydroxyl group when using peptide coupling conditions.

The derivatization of two sterically hindered amines was recently described by one of us (Scheme 6).<sup>55</sup> Chiral indoline carbamates **14**, obtained from asymmetric C(sp<sup>3</sup>)–H activation are liquid substances. Therefore, **14d–e** were deprotected to the N–H indolines **6d–e** and converted into the corresponding ferrocene carboxamides. Whereas **8d** could be prepared using classical conditions, **8e** required the generation of the lithium amide which was then reacted with ferrocenoyl chloride.

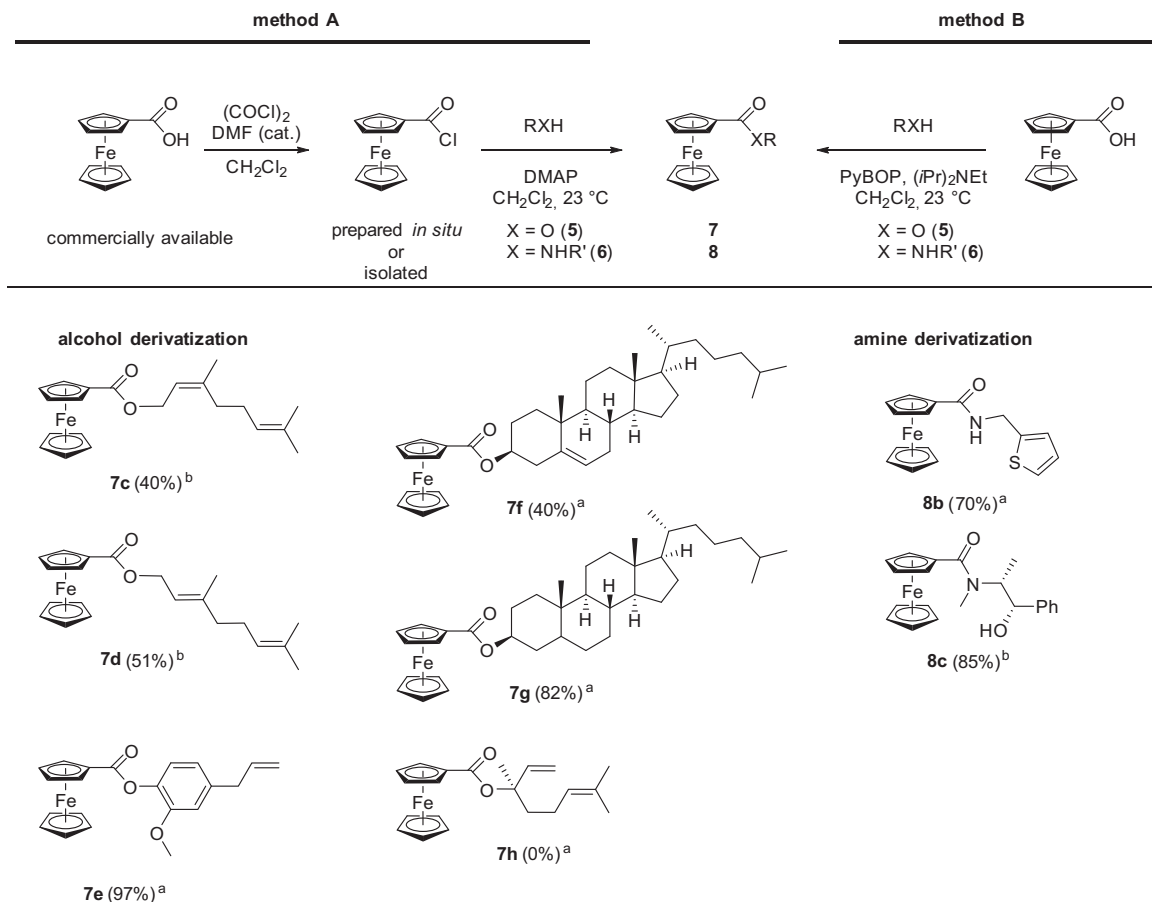
For all of the above described liquid molecules, we were able to obtain good single crystals through ferrocene derivatization. Crystal structures obtained were of high quality and allowed to assign the absolute configuration for all chiral molecules (*vide infra*).

### 3.1.3. Structures published by other groups

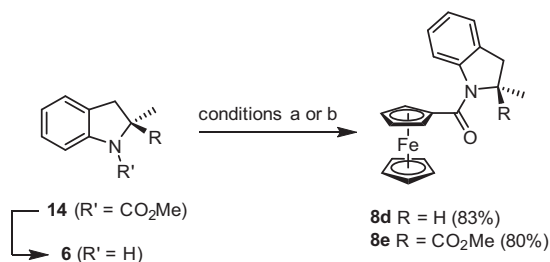
Shibata et al. used ferrocene derivatization with the aim of obtaining single crystals already in 2006. They described the first



**Scheme 4.** Investigation of the stereochemistry of a nucleophilic substitution in the context of the total synthesis of aeruginosins.<sup>47</sup>



**Scheme 5.** Ferrocene derivatization of representative liquid or chiral alcohol and amine substrates, reaction conditions: <sup>a</sup>method A, <sup>b</sup>method B.



**Scheme 6.** Preparation of tertiary ferrocenyl amides,<sup>55</sup> reaction conditions: (a) DMAP, <sup>i</sup>Pr<sub>2</sub>NEt, FcCOCl, CH<sub>2</sub>Cl<sub>2</sub>, (b) LiHMDS, THF, −78 °C, then FcCOCl, −10 °C.

two examples of ferrocene carboxylates which allowed X-ray diffraction analysis and established the absolute configurations of **7i–k**<sup>41</sup> (Fig. 1). In the following years, this process was applied to the chiral alcohols **7l–m** and the determination of their absolute configuration was reported.<sup>42,43</sup> Although some structures already contained a heavy atom, the ferrocene moiety helped in the recrystallization process. Burns et al. have applied the ferrocene derivatization to synthetic intermediates of the halogenated terpene (+)-halomon and found the ferrocene carboxylates “as being particularly valuable in cases where common benzoate and sulfonate derivatives fail to induce adequate crystallinity.”<sup>56</sup> The same group also prepared the polyhalogenated structures **7p–q** and studied their conformation in the solid state.<sup>57</sup> In both cases, the primary alcohol reacted selectively in the presence of a secondary alcohol. Brown et al. determined the absolute configuration of **7r**.<sup>58</sup> Magauer et al. determined the constitution of racemic **7s**<sup>59</sup> and

assigned the absolute configuration of **5t**, an intermediate in the total synthesis of (−)-cyclospenone,<sup>60</sup> via crystallization of the ferrocene carboxylate **7t**. The latter demonstrates that a sterically hindered neopentyl alcohol can be efficiently converted (70%) at room temperature.

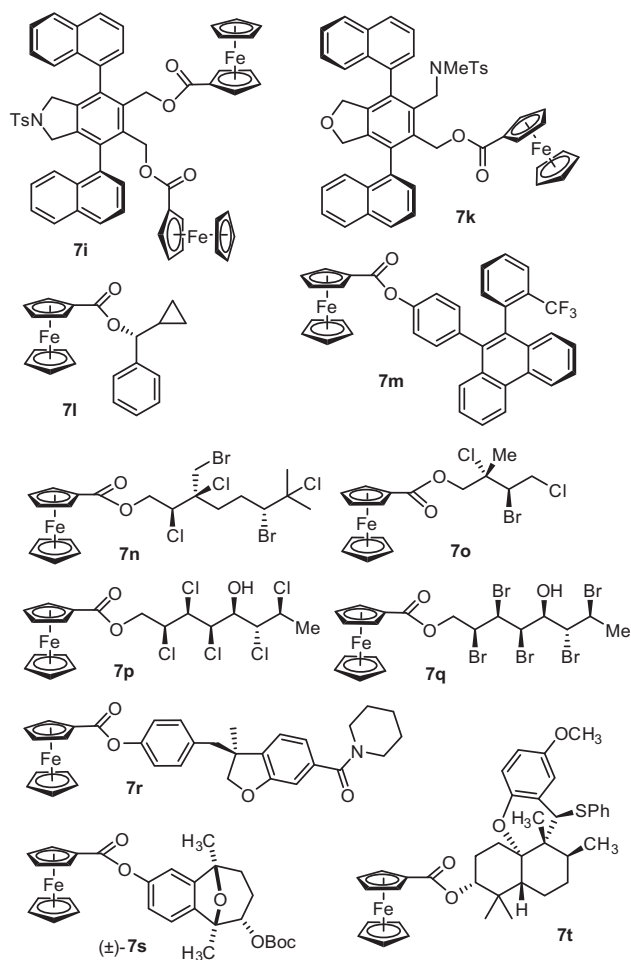
The independent applications by different international research groups underline that a powerful and operationally simple method to introduce a heavy atom containing moiety has been found.

## 3.2. Physical properties

### 3.2.1. Melting point

As discussed before, derivatization with *p*-nitrobenzoic acid has been used for a long time to deliver solids with sharp melting points from samples of poor crystallinity. A related, measurable effect is the increase in melting point that the *p*-nitrobenzoyl derivatization often induces. As a consequence it converts certain liquid samples into solids and thus allow for crystallization. In order to critically assess the utility of the ferrocene derivatization for liquid samples, we wanted to compare the melting points of ferrocene and *p*-nitrobenzoate derivatives of the same compound. Herein we have included the described compounds **5c–5f**, **6b–c** as well as the literature known derivatives **5u–z**, **6f–l**.<sup>49</sup>

In general, the melting points of both derivatives are relatively similar (Fig. 2). Geraniol **5d**, a component of essential oils, was converted from liquid to solid state by both derivatization approaches. Only sporadically, e.g., **5e**, **5v** or **6c**, marked differences between both derivatives can be noted. Although the comparison is of limited significance, it shows that ferrocene derivatization is as pow-



**Figure 1.** Further examples of successful utilization of ferrocene derivatization for crystallization.

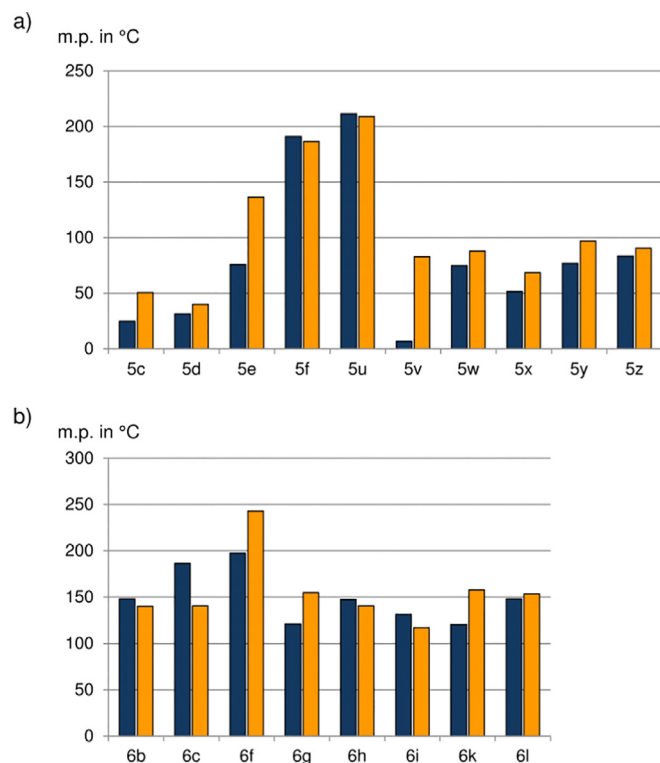
erful as *p*-nitrobenzoyl for the conversion of liquid samples **5c–e,v,w,z** and **6b,f–h,k** into solids.

### 3.2.2. Crystallographic data

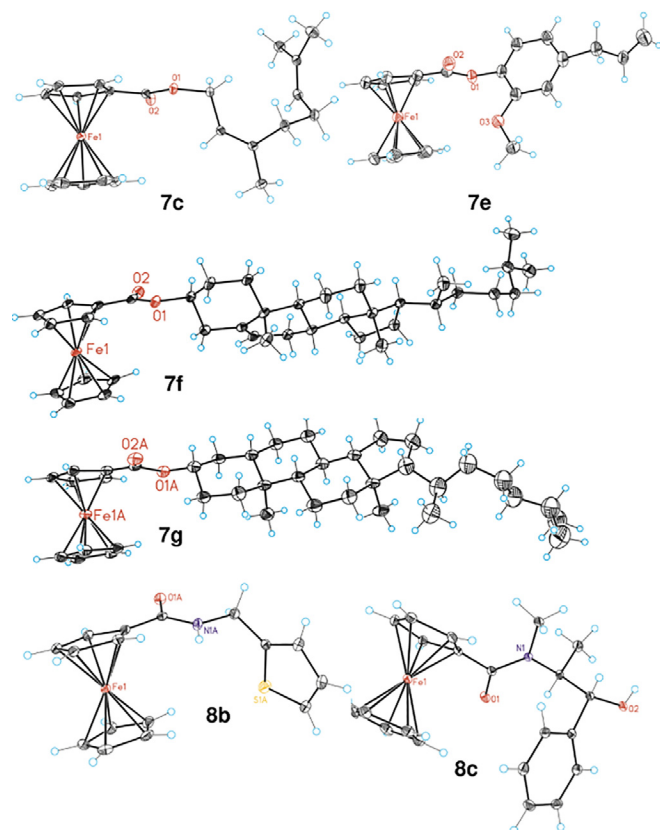
Single crystals suitable for X-ray diffraction analysis of **7c**, **7e–g** and **8b–c** were obtained by recrystallization. The ability to obtain crystal structure of **7c** and **7e** (Fig. 3) is particularly remarkable since the original compounds are oily liquids. Crystal structures of the steroid derivatives **7f–g** and ephedrine derivative **8c** are good examples of absolute configuration determination for compounds possessing only light atoms. Recrystallization was mostly carried out by vapor diffusion (for crystal structures in Fig. 3) and crystals with edge length  $\geq 0.5$  mm are not rare (Table 1). In some cases the crystal obtained was too large for a modern rotating anode with focusing mirrors and had to be cut to conduct the X-ray experiment.

The crystallographic data of the above described ferrocene derivatives are listed in Table 1. When structure factors of compounds previously reported in the literature were available, the structures were re-refined using SHELXL.<sup>61</sup> Since the methods of Parsons and Hooft improve the precision of the enantiopure distinguishing parameter in a similar way,<sup>62</sup> we calculated it using Parsons quotients here. Most crystal structures had excellent *R*<sub>1</sub> values ( $\geq 0.05$ ) with exception of **7m** (Table 1).

All crystal structures in Table 1 were measured on either MoK $\alpha$  or GaK $\alpha$  radiation and are characterized of excellent absolute structure parameters (Fig. 4). The limit for enantiopure compounds



**Figure 2.** Comparison of the melting points of (a) ester derived from alcohols **5** and (b) amides derived from amines **6** (orange: ferrocene derivatives, blue: *p*-nitrobenzoyl derivatives; average values are plotted for melting points which were reported as temperature ranges).<sup>49</sup>



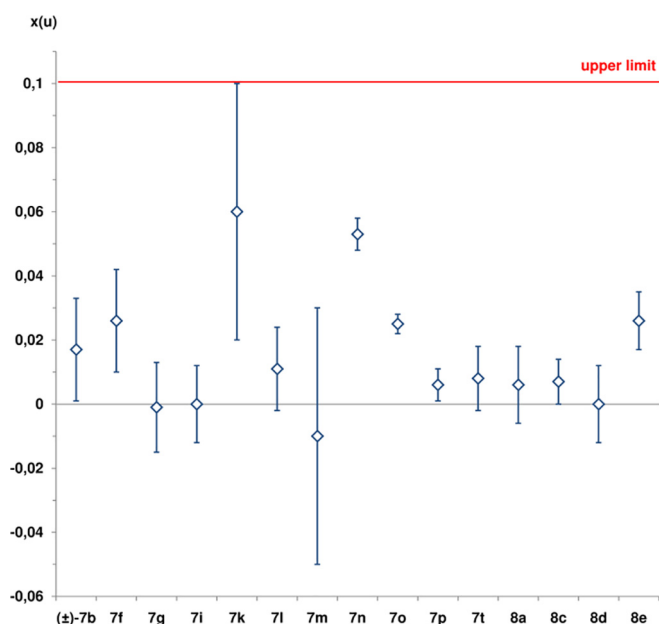
**Figure 3.** Crystal structures of **7c**, **7e**, **7f**, **7g**, **8b**, **8c** (Ortep representation with thermal ellipsoids at 50% probability).



**Table 1**

Crystal data obtained from new or previously reported ferrocene derivatives

No.	R1	wR2	GoF	Radiation type	Crystal system, space group	Crystal dimensions (mm <sup>3</sup> )	Flack $\chi^a$
( $\pm$ )- <b>7a</b> <sup>47</sup>	0.0499	0.0471	1.0423	MoK $\alpha$	Triclinic, $P\bar{1}$	0.47 $\times$ 0.38 $\times$ 0.12	—
( $\pm$ )- <b>7b</b> <sup>47</sup>	0.0468	0.1038	1.005	MoK $\alpha$	Monoclinic, $P2_1$	0.55 $\times$ 0.27 $\times$ 0.20	0.017(16) <sup>b</sup>
<b>7c</b>	0.0323	0.0799	1.080	MoK $\alpha$	Monoclinic, $P2_1/n$	0.40 $\times$ 0.04 $\times$ 0.02	—
<b>7e</b>	0.0532	0.1358	1.088	MoK $\alpha$	Triclinic, $P\bar{1}$	0.35 $\times$ 0.25 $\times$ 0.15	—
<b>7f</b>	0.0478	0.1283	1.059	MoK $\alpha$	Monoclinic, $C2$	0.10 $\times$ 0.05 $\times$ 0.03	0.026(16)
<b>7g</b>	0.0761	0.1870	1.014	MoK $\alpha$	Triclinic, $P1$	0.10 $\times$ 0.05 $\times$ 0.05	−0.001(14)
<b>7i</b> <sup>41</sup>	0.0435	0.1136	0.986	MoK $\alpha$	Monoclinic, $P2_1$	0.60 $\times$ 0.20 $\times$ 0.20	0.000(12) <sup>c</sup>
<b>7k</b> <sup>41</sup>	0.0856	0.2138	0.914	MoK $\alpha$	Orthorhombic, $P2_12_12_1$	0.40 $\times$ 0.40 $\times$ 0.10	0.06(4) <sup>c</sup>
<b>7l</b> <sup>42</sup>	0.0317	0.0745	1.019	MoK $\alpha$	Monoclinic, $P2_1$	0.80 $\times$ 0.50 $\times$ 0.40	0.011(13) <sup>c</sup>
<b>7m</b> <sup>43</sup>	0.1672	0.3666	1.001	MoK $\alpha$	Monoclinic, $P2_1$	0.75 $\times$ 0.29 $\times$ 0.18	−0.01(4) <sup>c</sup>
<b>7n</b> <sup>56</sup>	0.0533	0.1103	1.051	MoK $\alpha$	Monoclinic, $P2_1$	0.16 $\times$ 0.15 $\times$ 0.06	0.053(5)
<b>7o</b> <sup>56</sup>	0.0187	0.0478	1.032	MoK $\alpha$	Monoclinic, $P2_1$	0.27 $\times$ 0.18 $\times$ 0.08	0.025(3)
<b>7p</b> <sup>57</sup>	0.0228	0.0481	0.994	MoK $\alpha$	Triclinic, $P1$	0.29 $\times$ 0.09 $\times$ 0.04	0.006(5)
<b>7q</b> <sup>57</sup>	0.0301	0.0671	1.111	MoK $\alpha$	Monoclinic, $P2_1/n$	0.08 $\times$ 0.07 $\times$ 0.04	— <sup>d</sup>
( $\pm$ )- <b>7s</b> <sup>59</sup>	0.0412	0.0892	1.070	MoK $\alpha$	Triclinic, $P\bar{1}$	0.10 $\times$ 0.06 $\times$ 0.02	—
<b>7t</b> <sup>60</sup>	0.0447	0.0792	1.039	MoK $\alpha$	Monoclinic, $P2_1$	0.10 $\times$ 0.03 $\times$ 0.01	0.008(10)
<b>8a</b> <sup>44</sup>	0.0327	0.0818	1.109	MoK $\alpha$	Orthorhombic, $P2_12_12_1$	0.60 $\times$ 0.48 $\times$ 0.34	0.006(12) <sup>c</sup>
<b>8b</b>	0.0309	0.0809	1.039	MoK $\alpha$	Monoclinic, $P2_1/c$	0.20 $\times$ 0.15 $\times$ 0.10	—
<b>8c</b>	0.0225	0.0632	1.062	MoK $\alpha$	Monoclinic, $P2_1$	0.20 $\times$ 0.15 $\times$ 0.10	0.007(7)
<b>8d</b> <sup>55</sup>	0.0450	0.1192	1.096	GaK $\alpha$	Orthorhombic, $P2_12_12_1$	0.70 $\times$ 0.30 $\times$ 0.20	0.000(12)
<b>8e</b> <sup>55</sup>	0.0380	0.1098	1.040	GaK $\alpha$	Trigonal, $P3_2$	0.11 $\times$ 0.07 $\times$ 0.03	0.026 (9)

<sup>a</sup> Recalculated Flack parameter using the quotient method according to Parsons.<sup>b</sup> The racemic compound crystallized as conglomerate yielding an enantiopure crystal.<sup>c</sup> Originally published Flack parameter, see reference in column 1.<sup>d</sup> The compound with an optical purity of 80% ee<sup>57</sup> crystallized as racemate.**Figure 4.** Flack parameter using quotient method according to Parsons with 1 $\sigma$  uncertainty.

defined by Flack of  $x(u) \leq 0.1(1)$  was easily met and in most cases the parameter and its standard deviation were significantly smaller than the strong inversion-distinguishing power  $x \leq 0.04(4)$  defined by Flack.<sup>13</sup> In summary, the ferrocene derivatization of a variety of liquid chiral molecules allowed us to obtain single crystals suitable for X-ray crystallography, which enabled us to unambiguously assign the absolute configuration.

#### 4. Conclusion

We have outlined the concept of derivatizing small molecules with ferrocene carboxylic acid in order to obtain suitable crystals

for X-ray diffraction analysis. Seven new crystal structures of ferrocenyl ester and amides containing natural products and synthetic building blocks are reported. Together with previous applications in total syntheses and asymmetric catalysis, these examples underline that the derivatization of small molecules with ferrocene carboxylic acid is an operationally simple method to obtain crystals of good quality. The strength of this technique lies in the ability to convert liquid samples into solids and to introduce a heavy atom for absolute structure determination. The crystallographic data sets obtained are of high quality and all absolute structures were unambiguously determined using MoK $\alpha$  or GaK $\alpha$  radiation.

This method has been successfully applied in 23 cases, but we also experienced some limitations, as the derivatization of tertiary alcohols did not succeed in our hands. That said, the method was found to be superior to other derivatizations in some examples. It is based on a simple manipulation, standard equipment and a commercial reagent which makes it easily accessible for synthetic chemists. Further application in total synthesis and asymmetric synthesis are expected in the future.

#### 5. Experimental

##### 5.1. General

Ferrocene carboxylic acid (CAS: 1271-42-7) was purchased from Sigma Aldrich. Ferrocenoyl chloride<sup>63</sup> was prepared following standard protocol using oxalyl chloride in dichloromethane with a catalytic amount of DMF and stored in the glovebox. Alternatively, Ferrocenoyl chloride can be purchased from Sigma Aldrich (CAS: 1293-79-4). The reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA). Purifications were carried out on a Combi-Flash® Rf apparatus. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. NMR spectra were recorded at 23 °C on a Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatus. Mass spectra were recorded on a Waters LCT Premier Spectrometer. Melting points were determined using a Büchi melting point apparatus. Crystal structure

determination for compounds **7e**, **7f**, **7g**, **8b** and **8c** was carried out using a Rigaku diffractometer equipped with a Pilatus 200 K area detector, a Rigaku MicroMax-007HF microfocus rotating anode with MoK $\alpha$  radiation, Confocal Max Flux optics and an Oxford Cryosystems low temperature device Cryostream 700 plus ( $T = -173^\circ\text{C}$ ). Crystal structure determination for compound **7c** were carried out using a Apex DUO diffractometer equipped with a Kappa 4-axis goniometer, an APEX II 4K CCD area detector, a Microfocus Source E025 luS using MoK $\alpha$  radiation, Quazar MX multilayer Optics as monochromator and an Oxford Cryosystems low temperature device Cryostream 700 plus ( $T = -173^\circ\text{C}$ ). Crystal structures **7a–b**, **7i–t** and **8a** were reported previously and measured using MoK $\alpha$  radiation from various sources. Amides **8d–e** were also reported previously and measured on a Stoe StadiVari diffractometer equipped with a MetalJet D2+ 70 and a Pilatus 300K area detector using GaK $\alpha$  radiation. More detailed information on the X-ray experiments of all previously reported structures can be found in the references given in column 1 of Table 1. Crystal structures of **7c**, **7e–g** and **8b–c**, which are reported here for the first time, can be obtained free of charge from the Cambridge Crystallographic Data Centre under the deposit numbers 1568685–1568690.

## 5.2. Neryl ferrocene carboxylate **7c**

To a suspension of ferrocenecarboxylic acid (82 mg, 0.357 mmol, 1.1 equiv), nerol (50 mg, 0.324 mmol, 1.0 equiv), DMAP (7.9 mg, 0.065 mmol, 0.2 equiv) and DIPEA (0.113 mL, 0.648 mmol, 2.0 equiv) in DCM (2 mL) was added PyBOP (186 mg, 0.357 mmol, 1.1 equiv). The reactions mixture turned into an orange solution and was stirred at r.t. for 16 h. The reaction mixture was quenched with brine, diluted with EtOAc and the phases were separated. The aq. layer was extracted with EtOAc twice and the combined organic extracts were concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g SiO $_2$ , gradient: 0–3% EtOAc in CyHex) affording 47 mg (0.128 mmol, 40%) of an orange oil, which could be crystallized. Single crystals were obtained by vapor diffusion using Et $_2$ O (solvent) and ethanol (anti-solvent).  $^1\text{H}$  NMR (500 MHz, CDCl $_3$ )  $\delta$  5.49–5.43 (m, 1H), 5.17–5.12 (m, 1H), 4.82–4.79 (m, 2H), 4.71 (dd,  $J = 7.2, 0.8$  Hz, 2H), 4.39–4.35 (m, 2H), 4.19 (s, 5H), 2.23–2.17 (m, 2H), 2.16–2.10 (m, 2H), 1.79 (d,  $J = 1.2$  Hz, 3H), 1.70 (d,  $J = 0.9$  Hz, 3H), 1.63 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz, CDCl $_3$ )  $\delta$  171.6, 142.3, 132.2, 123.7, 119.8, 71.5, 71.2 (2C), 70.2 (2C), 69.7 (5C), 60.8, 32.3, 26.8, 25.7, 23.6, 17.7; mp: 50–51  $^\circ\text{C}$ ; HRMS-ESI: calculated for C $_{21}\text{H}_{26}\text{FeNaO}_2$  [M+Na] $^+$ : 389.1175; found: 389.1170.

## 5.3. Geranyl ferrocene carboxylate **7d**

To a suspension of ferrocenecarboxylic acid (16 mg, 0.071 mmol, 1.1 equiv), geraniol (10 mg, 0.065 mmol, 1.0 equiv), DMAP (1 mg, 0.008 mmol, 0.1 equiv) and Et $_3\text{N}$  (0.018 mL, 0.130 mmol, 2.0 equiv) in DCM (1 mL) was added PyBOP (37 mg, 0.071 mmol, 1.1 equiv). The reactions mixture turned into an orange solution and was stirred at rt for 16 h. The reaction mixture was quenched with brine, diluted with EtOAc and the phases were separated. The aq. layer was extracted with EtOAc twice and the combined organic extracts were concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g SiO $_2$ , gradient: 0–4% EtOAc in CyHex) affording 12 mg (0.033 mmol, 51%) of an orange oil which solidifies upon standing.  $^1\text{H}$  NMR (400 MHz, CDCl $_3$ )  $\delta$  5.48 (m, 1H), 5.16–5.10 (m, 1H), 4.83 (t,  $J = 1.9$  Hz, 2H), 4.76 (d,  $J = 7.0$  Hz, 2H), 4.40 (t,  $J = 1.9$  Hz, 2H), 4.22 (s, 5H), 2.21–2.06 (m, 4H), 1.81 (s, 3H), 1.71 (d,  $J = 0.7$  Hz, 3H), 1.63 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz, CDCl $_3$ )  $\delta$  171.7, 142.0, 131.8, 123.8, 118.9, 71.4, 71.2 (2C), 70.2 (2C), 69.7 (5C), 61.1,

39.6, 26.3, 25.7, 17.7, 16.6; mp: 39–41  $^\circ\text{C}$ ; HRMS-ESI: calculated for C $_{21}\text{H}_{26}\text{FeNaO}_2$  [M+Na] $^+$ : 389.1175; found: 389.1171.

## 5.4. Eugenyl ferrocene carboxylate **7e**

To a suspension of ferrocenecarboxylic acid (57.4 mg, 0.250 mmol, 1.4 equiv) in DCM (1 mL) were added oxalyl chloride (0.021 mL, 0.245 mmol, 1.3 equiv) and three drops of dry DMF at 0  $^\circ\text{C}$ . After the gas evolution ceased and the reaction mixture turned into a clear solution, it was stirred for 0.5 h at rt. Next, a solution of eugenol (30 mg, 0.183 mmol, 1.0 equiv) and DMAP (61 mg, 0.499 mmol, 2.7 equiv) in DCM (1 mL) was added and the reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched by adding a small amount of silica gel and concentrating to dryness. The crude product was purified by flash chromatography (12 g SiO $_2$ , gradient: 0–10% EtOAc in CyHex) affording 67 mg (0.178 mmol, 97%) of an orange solid. Single crystals were obtained by vapor diffusion using CH $_2\text{Cl}_2$  (solvent) and pentane (anti-solvent).  $^1\text{H}$  NMR (400 MHz, CDCl $_3$ )  $\delta$  7.03 (d,  $J = 8.0$  Hz, 1H), 6.89–6.80 (m, 2H), 6.02 (ddt,  $J = 16.8, 10.1, 6.7$  Hz, 1H), 5.19–5.10 (m, 2H), 5.01–4.97 (m, 2H), 4.53–4.48 (m, 2H), 4.37 (s, 5H), 3.90 (s, 3H), 3.43 (d,  $J = 6.7$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz, CDCl $_3$ )  $\delta$  169.9, 151.4, 138.9, 138.1, 137.3, 123.1, 120.9, 116.2, 112.9, 71.8 (2C), 70.8 (2C), 70.3, 70.2 (5C), 55.8, 40.2; mp: 136–137  $^\circ\text{C}$ ; HRMS-ESI: calculated for C $_{21}\text{H}_{20}\text{FeNaO}_3$  [M+Na] $^+$ : 399.0654; found: 399.0652.

## 5.5. Recovery of eugenol **5d** by saponification of **7d**

Eugenyl ferrocene carboxylate (25 mg, 0.066 mmol, 1.0 equiv) was added to test tube, dissolved in THF/ MeOH (0.7 mL, ratio 3:1) and cooled to 0  $^\circ\text{C}$ . At that temperature, an aqueous solution of lithium hydroxide (c 1 M, 0.4 mL, 0.396 mmol, 6.0 equiv) was added. The reaction mixture was allowed to warm up and stirred for 16 h at rt 600 mg silica were added and all volatiles were evaporated. The solid was loaded directly onto a column and purification by flash chromatography (12 g SiO $_2$ , 5–10% EtOAc in CyHex) gave 8.2 mg (0.050 mmol, 75%) of a pale yellow oil. Spectroscopic data are in agreement with the ones previously reported.<sup>64</sup>  $^1\text{H}$  NMR (500 MHz, CDCl $_3$ )  $\delta$  6.88–6.81 (m, 1H), 6.72–6.64 (m, 2H), 5.95 (ddt,  $J = 16.8, 10.0, 6.7$  Hz, 1H), 5.47 (s, 1H), 5.12–5.01 (m, 2H), 3.87 (s, 3H), 3.32 (dt,  $J = 6.6, 1.2$  Hz, 2H).

## 5.6. Cholesteryl ferrocene carboxylate **7f**<sup>50,51</sup>

Cholesterol (60.1 mg, 0.155 mmol, 1.0 equiv) and DMAP (22.0 mg, 0.180 mmol, 1.2 equiv) were weight in a small vial and a solution of ferrocenoyl chloride (56.0 mg, 0.225 mmol, 1.5 equiv) in 2 mL DCM was added dropwise and resulted in a deep red solution which was stirred at rt for 16 h. The reaction mixture was quenched by adding a small amount of silica gel and all volatiles were evaporated under reduced pressure. The crude product was purified by flash chromatography (12 g SiO $_2$ , gradient: 0–10% EtOAc in CyHex, flushing with 50% EtOAc in CyHex to recovered unreacted cholesterol) affording 36.5 mg (0.061 mmol, 40%) of an orange solid. 26.5 mg (0.069 mmol, 44%) of unreacted cholesterol were recovered. Single crystals were obtained by vapor diffusion using acetone (solvent) and pentane (anti-solvent).  $^1\text{H}$  NMR (500 MHz, CDCl $_3$ )  $\delta$  5.42 (d,  $J = 3.7$  Hz, 1H), 4.83–4.79 (m, 2H), 4.79–4.73 (m, 1H), 4.39–4.35 (m, 2H), 4.20 (s, 5H), 2.42 (m, 2H), 2.01 (m, 5H), 1.75–1.64 (m, 1H), 1.52 (m, 6H), 1.41–0.96 (m, 14H), 1.08 (s, 3H), 0.93 (d,  $J = 6.5$  Hz, 3H), 0.88 (d,  $J = 2.3$  Hz, 3H), 0.86 (d,  $J = 2.2$  Hz, 3H), 0.69 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz, CDCl $_3$ )  $\delta$  171.2, 139.9, 122.8, 73.7, 71.9, 71.3 (2C), 70.3 (2C), 69.9 (5C), 56.9, 56.3, 50.2, 42.5, 39.9, 39.7, 38.6, 37.2, 36.8, 36.3, 36.0, 32.1, 32.1, 28.4, 28.3, 28.2, 24.5, 24.0, 23.0, 22.7, 21.2, 19.6, 18.9, 12.0;

mp: 186–187 °C; HRMS-ESI: calculated for  $C_{38}H_{54}FeNaO_2$   $[M+Na]^+$ : 621.3366; found: 621.3367;  $[\alpha]_D^{26} = +4.7$  (c 0.5,  $CHCl_3$ ).

### 5.7. Cholestanyl ferrocene carboxylate 7g<sup>52</sup>

To a suspension of ferrocenecarboxylic acid (29.8 mg, 0.130 mmol, 2.0 equiv) in DCM (1 mL) were added oxalyl chloride (0.011 mL, 0.130 mmol, 2.0 equiv) and two drops of dry DMF at 0 °C. After the gas evolution ceased and the reaction mixture turned into a clear solution, it was stirred for 0.5 h at rt. Then, a solution of cholestanol (25.2 mg, 0.065 mmol, 1.0 equiv) and DMAP (39.6 mg, 0.650 mmol, 5.0 equiv) in DCM (1 mL) was added and the reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched by adding a small amount of silica gel and all volatiles were evaporated under reduced pressure. The crude product was purified by flash chromatography (40 g  $SiO_2$ , gradient: 0–10%  $Et_2O$  in Pentane) affording 32 mg (0.178 mmol, 80%) of an orange solid. Single crystals were obtained by slow evaporation of a solution of  $CH_2Cl_2$  and ethanol.  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  4.86 (tt,  $J = 11.2, 4.9$  Hz, 1H), 4.81–4.77 (m, 2H), 4.38–4.34 (m, 2H), 4.19 (s, 5H), 2.01–1.94 (m, 1H), 1.94–1.87 (m, 1H), 1.87–1.74 (m, 2H), 1.72–1.42 (m, 7H), 1.41–1.19 (m, 10H), 1.17–0.96 (m, 9H), 0.91 (d,  $J = 6.8$  Hz, 3H), 0.89–0.87 (m, 6H), 0.86 (d,  $J = 2.3$  Hz, 3H), 0.66 (s, 3H), 0.71–0.65 (m, 1H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  171.3, 73.4, 72.1, 71.2 (2C), 70.3, 70.2, 69.9 (5C), 56.6, 56.4, 54.4, 44.9, 42.8, 40.2, 39.7, 37.0, 36.3, 36.0, 35.7, 35.7, 34.5, 32.2, 28.9, 28.4, 28.2, 28.0, 24.4, 24.0, 23.0, 22.7, 21.4, 18.8, 12.5, 12.2; mp: 191–192 °C; HRMS-ESI: calculated for  $C_{38}H_{56}FeNaO_2$   $[M+Na]^+$ : 623.3523; found: 623.3531;  $[\alpha]_D^{26} = +22.0$  (c 0.5,  $CHCl_3$ ).

### 5.8. N-(Thiophen-2-ylmethyl)ferrocenyl amide 8b

To a suspension of ferrocenecarboxylic acid (73 mg, 0.319 mmol, 1.1 equiv) in DCM (1 mL) were added oxalyl chloride (0.027 mL, 0.319 mmol, 1.1 equiv) and three drops of dry DMF at 0 °C. After the gas evolution ceased and the reaction mixture turned into a clear solution, it was stirred for 0.5 h at rt. Next, a solution of thiophen-2-ylmethanamine (32.8 mg, 0.290 mmol, 1.0 equiv) in DCM (0.5 mL) and DIPEA (0.101 mL, 0.580 mmol, 2.0 equiv) were added and the reaction mixture was stirred for 16 h at rt. The reaction mixture was quenched by adding a small amount of silica gel and concentrating to dryness. The crude product was purified by flash chromatography (12 g  $SiO_2$ , gradient: 0–30% EtOAc in CyHex) affording 66 mg (0.203 mmol, 70%) of a brown solid. Single crystals were obtained by vapor diffusion using  $CH_2Cl_2$  (solvent) and pentane (anti-solvent).  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.25–7.28 (m, 1H), 7.06 (m, 1H), 6.99 (dd,  $J = 5.3, 3.5$  Hz, 1H), 5.98 (br s, 1H), 4.76 (d,  $J = 5.8$  Hz, 2H), 4.64–4.71 (m, 2H), 4.33–4.39 (m, 2H), 4.19 (s, 5H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  170.3, 141.7, 127.0, 126.0, 125.2, 75.7, 70.7 (2C), 69.8 (5C), 68.3 (2C), 38.4; mp: 139–141 °C; HRMS-ESI: calculated for  $C_{16}H_{15}FeNNaOS$   $[M+Na]^+$ : 348.0116; found: 348.0123.

### 5.9. N-((1R,2S)-1-Hydroxy-1-phenylpropan-2-yl)-N-ferrocenyl amide 8c

To a suspension of ferrocenecarboxylic acid (49 mg, 0.212 mmol, 1.0 equiv), (–)-ephedrine (35 mg, 0.212 mmol, 1.0 equiv), and DIPEA (0.12 mL, 0.424 mmol, 2.0 equiv) in DCM (2 mL) was added PyBOP (110 mg, 0.212 mmol, 1.0 equiv). The reaction mixture turned into an orange solution and was stirred at rt for 16 h. The reaction mixture was quenched with brine, diluted with EtOAc and the phases were separated. The aq layer was extracted with EtOAc twice and the combined organic extracts were concentrated under reduced pressure. The crude product was purified by flash chromatography (12 g  $SiO_2$ , gradient: 0–50%

EtOAc in CyHex) affording 68 mg (0.180 mmol, 85%) of an orange solid. Single crystals were obtained by vapor diffusion using THF (solvent) and cyclohexane (anti-solvent). Due to the presence of conformers, the NMR analysis had to be carried out at 393 Kelvin. Due to the conformational effects, some  $^{13}C$  NMR signals contain shoulders, others are of weak intensity.  $^1H$  NMR (500 MHz,  $DMSO-d_6$ , 393 K)  $\delta$  7.32 (m, 4H), 7.24 (m, 1H), 5.02 (d,  $J = 4.3$  Hz, 1H), 4.71 (m, 1H), 4.50 (m, 1H), 4.45 (br s, 1H), 4.40 (br s, 1H), 4.28 (br s, 2H), 4.12 (s, 5H), 2.95 (s, 3H), 1.24 (d,  $J = 6.7$  Hz, 3H);  $^{13}C$  NMR (126 MHz,  $DMSO-d_6$ , 393 K)  $\delta$  168.7, 143.1, 127.0, 126.2, 125.8, 79.6, 74.4, 70.0, 68.7, 67.9, 56.2, 31.0, 12.3; mp: 140–141 °C; HRMS-ESI: calculated for  $C_{21}H_{24}FeNO_2$   $[M+H]^+$ : 378.1151; found: 378.1157;  $[\alpha]_D^{26} = -89.4$  (c 1.0,  $CHCl_3$ ).

### Acknowledgements

This work was supported by MINECO/FEDER, UE (Grant CTQ2016-75960-P to A.M.E.), MINECO-Severo Ochoa Excellence Accreditation 2014–2018 (Grant SEV-2013-0319 to A.M.E.), and the CERCA Program/Generalitat de Catalunya. We thank Imma Escofet (ICIQ) for determining optical rotations and for additional experiments. Guillaume Pilet (Université Claude Bernard Lyon 1) and Markus Neuburger (University of Basel) are gratefully acknowledged for providing X-ray structure factors of **8a**, **7a–b** and **8d–8e**, respectively.

### A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetasy.2017.09.002>.

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