A Potentially Limitless Chiral Pool *via* Conglomerate Crystallisation: Unidentified Spontaneous Resolution in the CSD.

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Dedicated to Jean Jacques, André Collet, and Samuel H. Wilen, for their work in cataloging conglomerate crystallisations.

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Supporting information for this article is given via a link at the end of the document.

Abstract: Conglomerate crystallisation is the behaviour responsible for spontaneous resolution and the discovery of molecular chirality by Pasteur. The phenomenon of conglomerate crystallisation of chiral organic molecules has been left largely undocumented and offers synthetic chemists a potential new chiral pool not reliant on biological systems to supply stereochemical information. While other crystallographic behaviours can be interrogated by automated searching, conglomerate crystallisations are not identified within the Cambridge Structural Database (CSD) and are therefore not accessible by conventional means. By conducting a manual search of the CSD, a list of over 1,700 chiral species capable of conglomerate crystallisation was curated by inspection of the synthetic routes described in each publication. The majority of these are produced by synthetic chemists who seldom note and rarely exploit the implications this phenomenon can have on the enantioenrichment of their crystalline materials. We propose that this list represents a limitless chiral pool which will continually grow in size as more conglomerate crystals are synthesised and recorded through the combined efforts of the synthetic and crystallographic communities.

Introduction

Asymmetric synthesis is only possible due to the homochiral nature of biological systems. The natural chiral pool is fixed in size, constrained by evolutionary pressures of the organisms that produce its members, and limited in scaffold diversity. Due to the homochirality of biological machinery and their chemical precursors, often the resulting compounds are only naturally available in one enantiomeric form. Yet, synthetic chemists have used the chiral pool to great effect with increasing levels of stereocontrol (**Figure 1**).[1,2] Firstly, by using the chiral pool as a synthetic feedstock, new enriched derivatives are accessible, expanding the library of available enantioenriched materials. Exploiting this expanded library to mediate diastereoselective syntheses allows for the transfer of stereochemical information from the chiral pool to new, previously inaccessible stereogenic elements. However, this reliance on the chiral pool to supply chemical scaffolds can limit access to a singular enantiomeric form of a product. The solution to this problem comes with the development of resolution methods using materials derived from the chiral pool, allowing for the separation of racemic non-natural materials and therefore granting access to both senses of enrichment of targets. Temporary attachment of these materials and their derivatives, so called chiral auxiliaries, to molecular frameworks allows for stereoselective transformations on substrates not part of the chiral pool. Auxiliaries can be designed to provide both senses of induction. However, this strategy requires derivatisation of the molecule, installing stoichiometric amounts of chiral information in a covalent fashion. Finally, modern asymmetric catalytic processes take these enriched materials and employs them in transformations which impart stereochemical bias whilst only requiring sub-stoichiometric amounts of the enriched material to be present, allowing chiral information to be amplified. Ultimately, all resolution agents, auxiliaries, chiral HPLC stationary phases, ligand scaffolds, catalysts and their possible derivatives used for accessing enantioenriched synthetic products *all rely on the chiral information imparted from biology*.[3]

Ideally chemists would not be solely reliant on biological systems for the creation of the chiral pool. If a chemist had control over the creation of their chiral pool, what traits would they ensure for their source of chirality? Firstly, it would contain chiral materials which would be of synthetic interest to them either as precursors or as catalysts/ligands. Such materials in this pool would be abundant and economically viable to obtain at both small and large scales. The materials in this pool would not be the result of evolutionary pressures of an organism and should not have a limited range of scaffolds. Ideally both enantiomers of each compound should be accessible to grant the greatest flexibility to the chemist. Finally, the pool would not be fixed in size and the chemical community would be responsible for increasing the chemical space available within this pool.

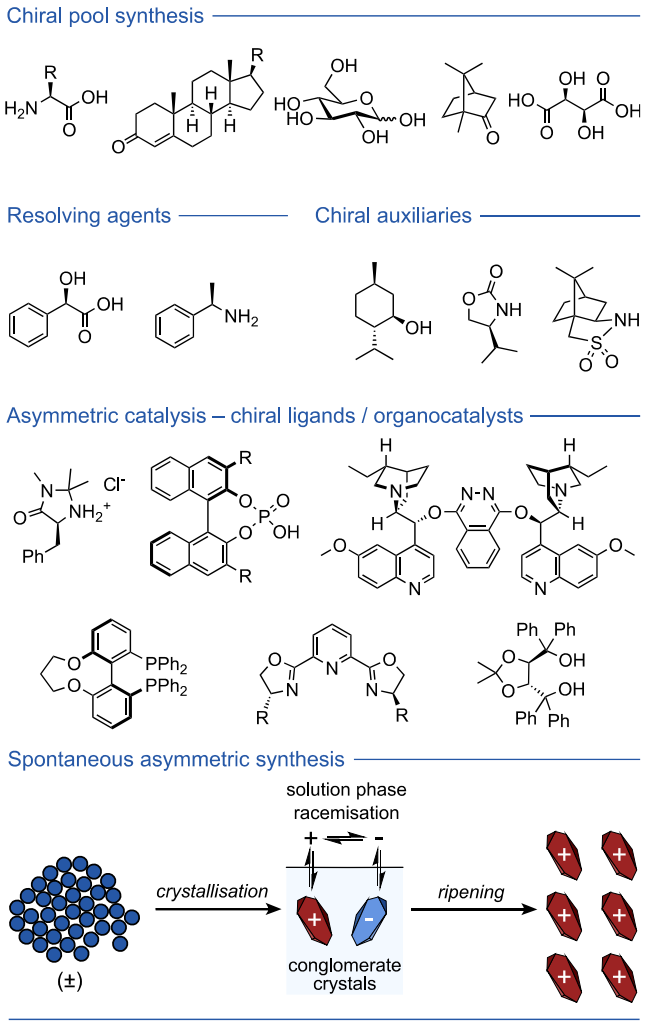


Figure 1. Strategies for asymmetric synthesis

There is an opportunity to create such a new chiral pool independent of biological information, based on the crystallographic properties of the material itself. A chiral pool which is unlinked from biological systems, containing diverse scaffolds, and has the potential for continuous expansion over time. The crystallographic phenomenon responsible for this possibility is called a conglomerate crystallisation. Racemic compounds do not always crystallise as racemic crystals. In the case of conglomerate crystals, a material can spontaneously resolve with each crystal containing a single enantiomer within its crystal structure.[†] The use of conglomerate crystallisation is historically important in the discovery of molecular chirality by Pasteur, with the first spontaneous resolution of tartrate salts.[4] By combining the chiral information imparted by conglomerate crystallisation, with chemical racemisation and a symmetry breaking event (either random or biased) crystals of a single enantiomorph can be ripened from the bulk material. With careful control of the crystallisation/racemisation conditions, full deracemisation of the bulk material can be achieved, with minimal external chiral influence i.e. a spontaneous asymmetric synthesis. The most common method to achieve this is an attrition-enhanced deracemisation, more commonly known as Viedma ripening.[5,6] The first attrition-enhanced deracemisation of conglomerate crystals was performed on sodium chlorate and sodium bromate salts.[7–10] This process has also been exploited to produce enantioenriched chiral organic molecules.[11–40] These conglomerate crystals represent a means to create a new chiral pool as their behaviour can be exploited by chemists to produce enantioenriched materials with no input from pre-existing natural sources.

Many of the desirable traits for an idealised chiral pool can be achieved using materials which undergo conglomerate crystallisation. There is no limit to which materials could crystallise as a conglomerate. There should be a vast range of diverse scaffolds which can crystallise in this manner. A conglomerate crystal is not dependent on a particular organism to produce an abundance of a desired compound to be economically viable. Practically speaking, both enantiomers are equally likely to crystallise, unless a specific enantiomer is deliberately biased from the crystallisation using a seed crystal, allowing access to both enantiomeric forms of all the compounds in this chiral pool. By combining conglomerate crystallisation as a source of chiral information, with racemisation conditions, and a symmetry breaking event, spontaneous asymmetric synthesis of members of this pool can be achieved. As chemists continue to synthesise and crystallise new materials, more conglomerate crystals should be discovered every year, thus increasing the structural diversity present in this enantioenriched library. Given these advantages, why is the phenomenon of conglomerate crystallisation not currently being exploited for spontaneous asymmetric synthesis as a means to generate this new chiral pool?

The answer is the lack of documentation. The main hurdle in the adoption of this strategy for asymmetric synthesis is the lack of curated knowledge of which crystals have the capacity to crystallise as conglomerates. The CSD (Cambridge Structural Database) is the largest and most widely adopted crystallographic repository service which is charged with the curation of crystallographic data produced by chemists. At the time of writing, it currently boasts over 1.1 million structures which can be searched and freely accessed by the community. The development of automated means to search this database with CCDC developed software (*ConQuest*) and community developed algorithms[41] have led to new insights on statistical crystal behaviours.[42,43] However, the CSD does not require conglomerate crystallisation behaviour to be identified in their metadata at submission, leading to a loss of this information as a search term in the database. Nor can a conglomerate crystallisation be predicted. Whilst efforts to rationalise conglomerate crystallisation have been conducted using crystal structure predication[44] structural modifications,[45–47] and supramolecular interactions,[48,49] currently only direct measurements of the physical characteristics of a crystal can identify conglomerate behaviour conclusively.

The typical work-flow of how X-ray crystallography samples are solved in most academic institutions is not conducive to the communication of conglomerate behaviour between the synthetic chemist and the crystallographer, symptomatic of a traditional view of separated scientific disciplines. Often the synthetic chemist will supply a crystal sample with a proposed structure and the solvent of crystallisation. Communication of the synthetic origin of the sample are less standardized and whether the

[†] Achiral molecules can also crystallise in Sohncke space groups as conglomerate crystals. In this paper we focus on conglomerate crystals originating from chiral organic materials as these are of greater interest for the synthetic community.

starting materials are racemic or enriched, possibly unclear. Without this information it is impossible for the crystallographer to unambiguously identify conglomerate behaviour. The sample will then be solved and returned to the synthetic chemist, who is generally interested in the connectivity of the molecule and relative stereochemistry within the crystal (unless they specifically ask for confirmation of absolute configuration). The importance of Sohncke space groups[50] or Flack parameters[51] in their crystallographic data has the potential to be overlooked by the synthetic community leading to the possibility of conglomerate behaviour being unidentified. The CIF (crystallographic information file) is deposited in the CSD by the crystallographer and now the synthetic chemist, crystallographer and the wider chemistry community are unaware of the full crystallographic behaviour of this sample. Once deposited, the conglomerate crystal can no longer be retrieved selectively without also bringing up thousands of non-conglomerate crystals which have been produced by enantioselective means. Therefore, this foundational phenomenon for the discovery of molecular chirality is currently being undocumented by both the synthetic and crystallographic communities.

It is only once a phenomenon has been documented that it can be fully exploited for its true potential by members of the synthetic community. The most complete list of potential conglomerate crystals was compiled by Jacques, Collet, and Wilen in their influential book published in 1981,[52] however this list predates the CSD. There is no actively curated list of chiral conglomerate crystals available in the literature. It is also understood that an automated search of the CSD to identify conglomerate crystallisation cannot be achieved without prior recording of metadata, that is to say, conglomerates are hiding in plain sight within the CSD. The wealth of crystallographic information present in the CSD represents an untapped resource for confirmed conglomerate behaviour. A manual search of crystals in the CSD would have to be conducted, which would interrogate the origin of each chiral crystal to ensure it originated from a racemic synthetic process. This requires manually examining each reported synthetic route. We sought to tap into the wealth of crystallographic and synthetic potential by conducting such a manual search of the CSD for previously unidentified conglomerate crystallisations in order to catalogue this new chiral pool.

Results and Discussion

The full list of conglomerate crystals along with their chemical structures and associated references are available in the *Supporting Information*. While the formation of chiral conglomerate crystals from achiral materials is also possible,[12,53–55] this work focussed specifically on documenting the spontaneous resolution phenomenon for chiral organic molecules which will be of interest for the synthetic community. The queries generated to conduct the search is detailed in the *Experimental* section. Once a list of candidates (21,098 crystals) was generated from search queries of the CSD mediated by *ConQuest*, a manual search and interpretation of the reported syntheses for the crystals within the CSD was undertaken to identify conglomerate crystals.

Caution had to be taken to distinguish between absolute and relative stereochemistry and the use of stereochemical notation to display perspective in compound representations. Crucially, confirming if a crystal had displayed conglomerate behaviour relied on the ability to trace the stereochemical enrichment of the starting materials and rule out any use of enantioselective methodology throughout the synthesis. In cases where the synthetic route for the compound was not available, or the described synthetic route was ambiguous in stereochemical information of the precursors, these examples were omitted. As such, all structures which were only available as a *CSD communication* were excluded as the origins of these materials was not possible to interrogate. Of course, the following assumptions had to be made while interpreting the reported syntheses and crystallisations within this list. It is assumed that the authors have reported the syntheses and the nature of the enrichment of their reagents/catalysts accurately, that the crystal structure(s) they reported indeed were crystallised from the batch of material as described and that the crystal structures themselves have been solved accurately (i.e. the space groups are correctly assigned).

From this search, 1,626 conglomerates were found within the CSD. A further 139 conglomerates were compiled from literature searches from known conglomerate crystallisations. A recent analysis of the CSD in 2020 by Rekis[42] suggests that 9.5% of the chiral compounds which crystallised in Sohncke space groups would be conglomerates, giving an estimated 4,281 conglomerates of chiral organic compounds hidden in the CSD. If this estimate is correct, the list curated in this work accounts for 41% of the chiral organic conglomerates currently unaccounted for in the CSD. In comparison, only 17 entries in the CSD have conglomerate behaviour identified within the deposited CIF. An intriguing question arises from this search – *how many*

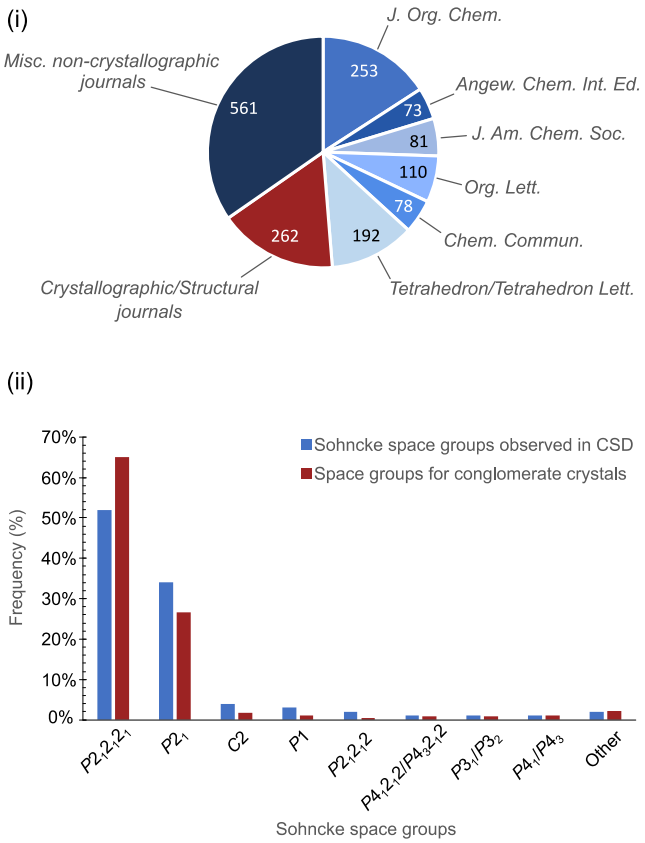


Figure 2. (i) The breakdown of journals which host conglomerate crystals. (ii) The comparison of space groups in the CSD and space groups that conglomerates crystallise within.

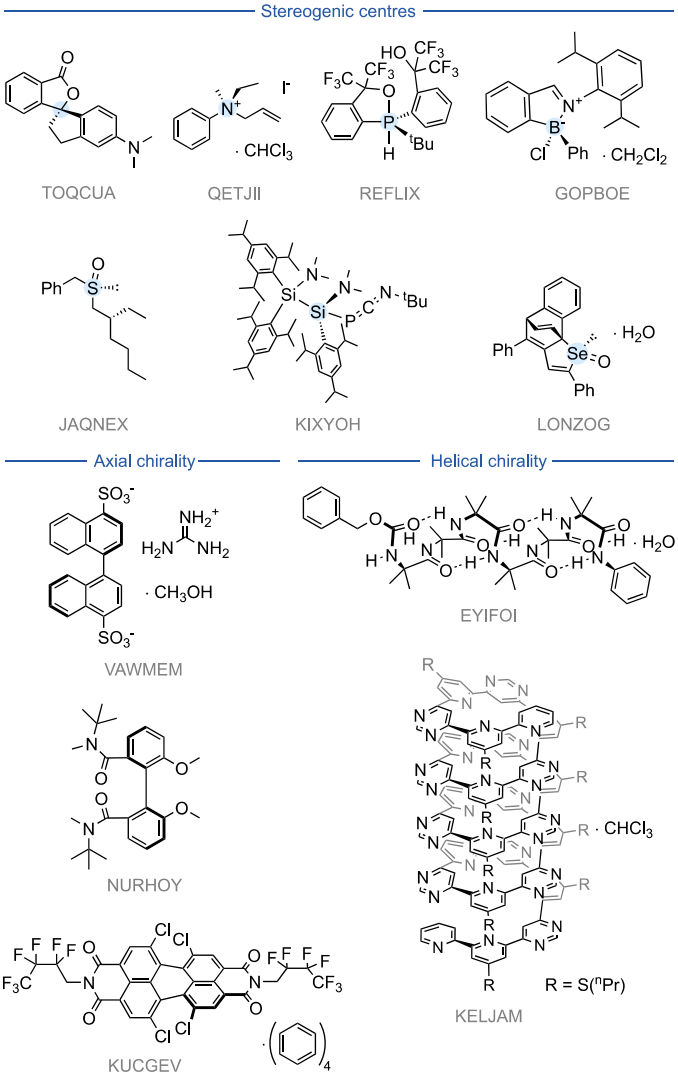


Figure 3. Types of stereocentres resolved by conglomerate crystallisation and other chiral elements present in conglomerate crystals.

compounds which have been prepared in a non-racemic fashion, and thus were excluded from this list, would show conglomerate behaviour? This includes molecules isolated from natural sources, pharmaceuticals, ligands, organocatalysts, peptide oligomers – most of which have only been prepared in an enantiomerically enriched form, and so any conglomerate behaviours would remain obscured.

The majority of the conglomerate crystals found from our search had been originally reported in synthetic groups publishing in non-crystallographic journals. A breakdown of the literature sources of conglomerate crystals is shown in **Figure 2** (i). Non-crystallographic journals made up 84% of this conglomerate list. It appears that synthetic chemists publishing in *J. Org. Chem.*, *Org. Lett., Tetrahedron,* and *Tetrahedron Lett.* are responsible for 34% of the papers containing conglomerate crystals. In almost all cases where a conglomerate appears in a synthesis focused paper, the phenomenon is not commented on in the CIF or the respective paper. Of the 1,626 conglomerates found in the CSD dataset, only 120 mentioned conglomerate behaviour in the manuscript text.

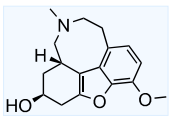
Conglomerates have no distinguishing features in their routinely recorded crystallographic metadata which identify them from other enantioenriched compounds. A comparison of the frequency of space groups present in conglomerate crystals (n = 1,765; red chart) and the frequency of Sohncke space groups in the CSD (n = 39,894; blue chart)[42] was conducted (**Figure 2** (ii)). While there is a slightly greater prevalence of $P2_12_12_1$ within the conglomerate dataset (65%) than observed in the CSD (52%), the overall trends of space group frequency of conglomerates match those observed in the CSD. The implications of this are clear: once a crystal is deposited in a crystallographic database (such as the CSD) under the current processes, only a manual review of the synthetic route to the compound will be able to identify a conglomerate.

Conglomerate behaviour was observed in all manner of chiral compounds, with no apparent limiting factors on what structures can undergo this process. Carbon, nitrogen, phosphorous, boron, sulfur, silicon, and selenium based stereocentres were among the compounds resolved by conglomerate behaviour (**Figure 3**). Other stereogenic elements are also possible to enrich by crystallisation, including axial chirality in the form of atropisomeric (VAWMEM,[56] NURHOY[57]) and twisted structures (KUCGEV[58]). Larger supramolecular examples also demonstrate the potential to be a conglomerate crystal, including a helical Aib_6 foldamer (EYIFOI[59]) and a helical pyridine-pyrimidine superstructure (KELJAM[60]). These demonstrate the diversity of structures which are within this list of conglomerate crystals.

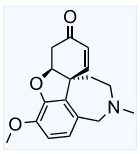
Structural complexity is not a barrier to conglomerate behaviour. Since natural product synthesis has been a core area of study for organic chemists for decades, we wished to pay special attention to conglomerate crystals discovered in this area. We have noted a number of natural products and related scaffolds that exhibit conglomerate behaviour when prepared in racemic fashion and crystallised (**Figure 4**). Notably, in these examples, the authors rarely note that spontaneous resolution had occurred during crystallisation. There were also notable examples of conglomerate crystals appearing within the synthetic routes of racemic total syntheses. For example, in the synthetic routes to Pallambin C/D[61] and Pyrenolide B,[62] both routes contained two structures which crystallised as conglomerates within the synthesis. This established that in some synthetic routes there can be multiple instances of conglomerate behaviour. The number of observed conglomerate crystals in natural products will be underestimated in this list as it was assumed that any material extracted from a biological source would be enantioenriched and so were discounted. Synthetic chemists have also been incentivised to produce enantioselective routes to natural products, which would also obscure conglomerate crystals. With these routes to racemic natural products already established, the use of a conglomerate crystallisation resolution or the development of racemisation conditions to allow for attrition-enhanced deracemisation within these established routes would give access to enantioenriched natural products.

Conglomerate behaviour is not restricted to compounds of academic interest. Materials exhibiting conglomerate behaviours with importance in medicinal chemistry were also compiled (**Figure 5**), as these compounds have proven industrial interest. The development of a crystallisation based spontaneous asymmetric synthesis of pharmaceuticals may be of interest because of the scalability of crystallisation processes, the already present need to find and control crystal polymorphs of the target, and the possibility of removing expensive and toxic transition metal based asymmetric catalysts from synthetic routes. Similar

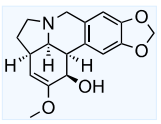
Natural products which are conglomerates



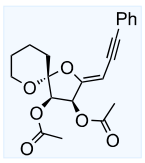
LOPJUX
isomer of Galanthamine
Lan *et al.* (2014)



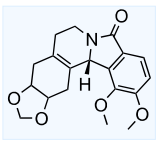
Narwedine
Shieh *et al.* (1994)



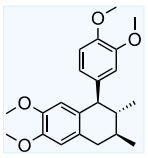
UNOJAK
Amarbellisine
Liu *et al.* (2012)



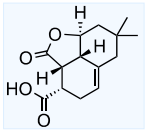
HOQSIQ
cis isomer of product from Chrysanthenum boreale
Robertson *et al.* (2008)



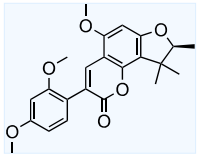
WIWYAD
Nuevamine
Wakchaure *et al.* (2008)



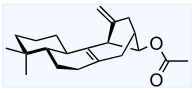
VIQCEF
Galbulin
Peng *et al.* (2013)



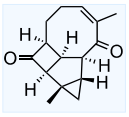
XEXNAP
isomer of Angucyclinones
Brinkworth *et al.* (1999)



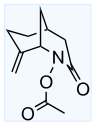
LUJHAB
Glycyfuranocoumarin A
Bojase *et al.* (2008)



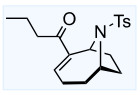
EHATEO
Jungermannenone scaffold
Liu *et al.* (2016)



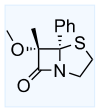
TAKBUF
Naupliolide
Abe *et al.* (2016)



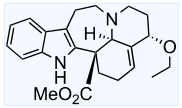
CEJWUM
Morphan scaffold
Zhai *et al.* (2017)



YEFMON
Tosyl propyl Anatoxin A
Roe *et al.* (2009)

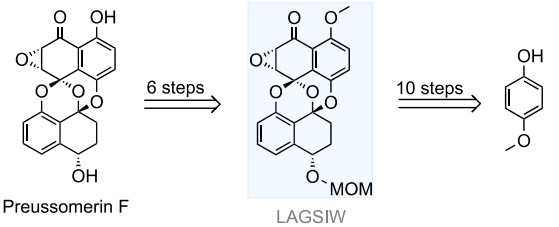


CEXYOT
Penam core
Hegedus *et al.* (1984)

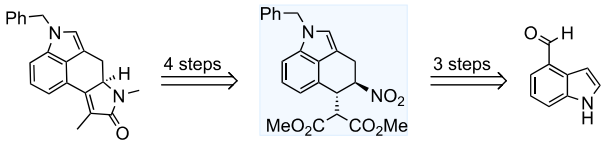


YOLROI
Andransinine
Low *et al.* (2004)

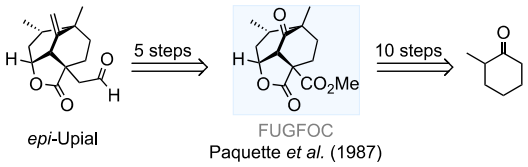
Conglomerates in total syntheses



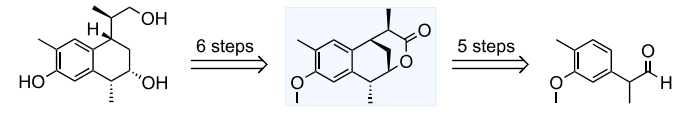
Preussomerin F
LAGSIW
Quesada *et al.* (2004)



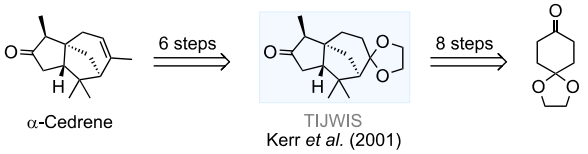
cycloclavine scaffold
TIGVOX
Chen *et al.* (2018)



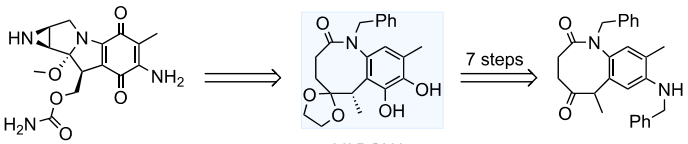
epi-Upial
FUGFOC
Paquette *et al.* (1987)



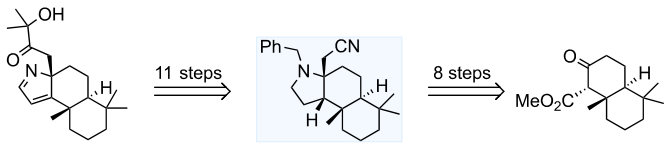
Trihydroxycalamenene
OMUMEP
Sun *et al.* (2010)



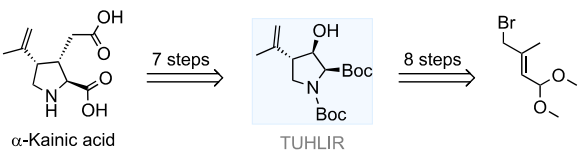
α-Cedrene
TIJWIS
Kerr *et al.* (2001)



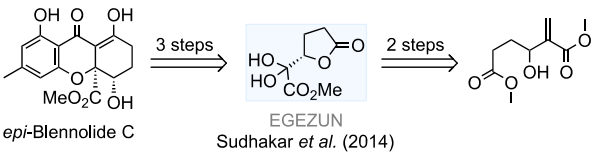
Mitomycin C
VABGUA
Yoshida *et al.* (1988)



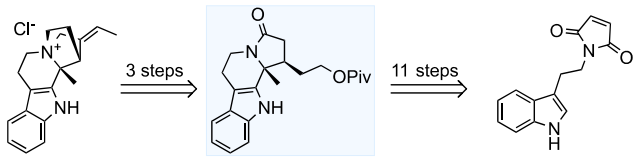
Chamobtusin A
UVAXAR
Suzuki *et al.* (2011)



α-Kainic acid
TUHLIR
Bachi *et al.* (1996)



epi-Blennolide C
EGEZUN
Sudhakar *et al.* (2014)



epi-Subnicanadine C
DIJBEG
Kalshetti *et al.* (2018)

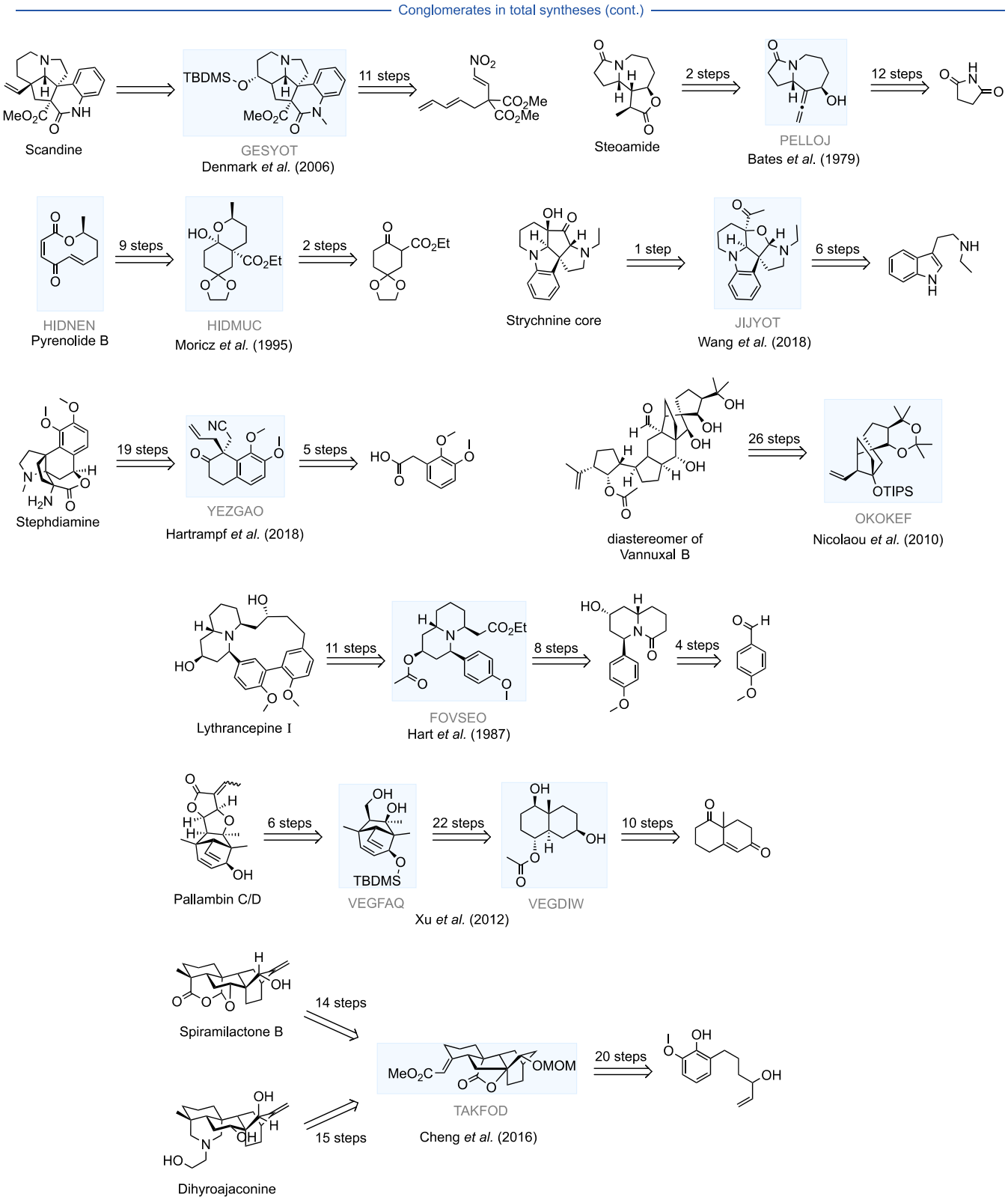


Figure 4. Natural products and total syntheses which contain a conglomerate crystal.

to the study of natural product conglomerate behaviour, the position of the conglomerate can occur at any stage in the synthesis.

The synthetic chemist does not need to rely on the serendipity of finding a conglomerate – they can be engineered. Exploring different crystallisation methods and conditions can produce conglomerate crystals from structures which previously did not show conglomerate crystallisation behaviours. This is a method to remove the probabilistic nature of conglomerate formation and allow for more control over which substrates display this behaviour. The use of crystal engineering can be used to formulate co-crystallisation conditions which lead to conglomerate crystal structures (HEGGAD,[63,64] NUMZUT,[65] UHUCEH,[66] and others[67–70]), while retaining favourable biophysical properties. For better or worse, this may also offer a means to evergreen patents on existing pharmaceuticals if a synthetic route is altered

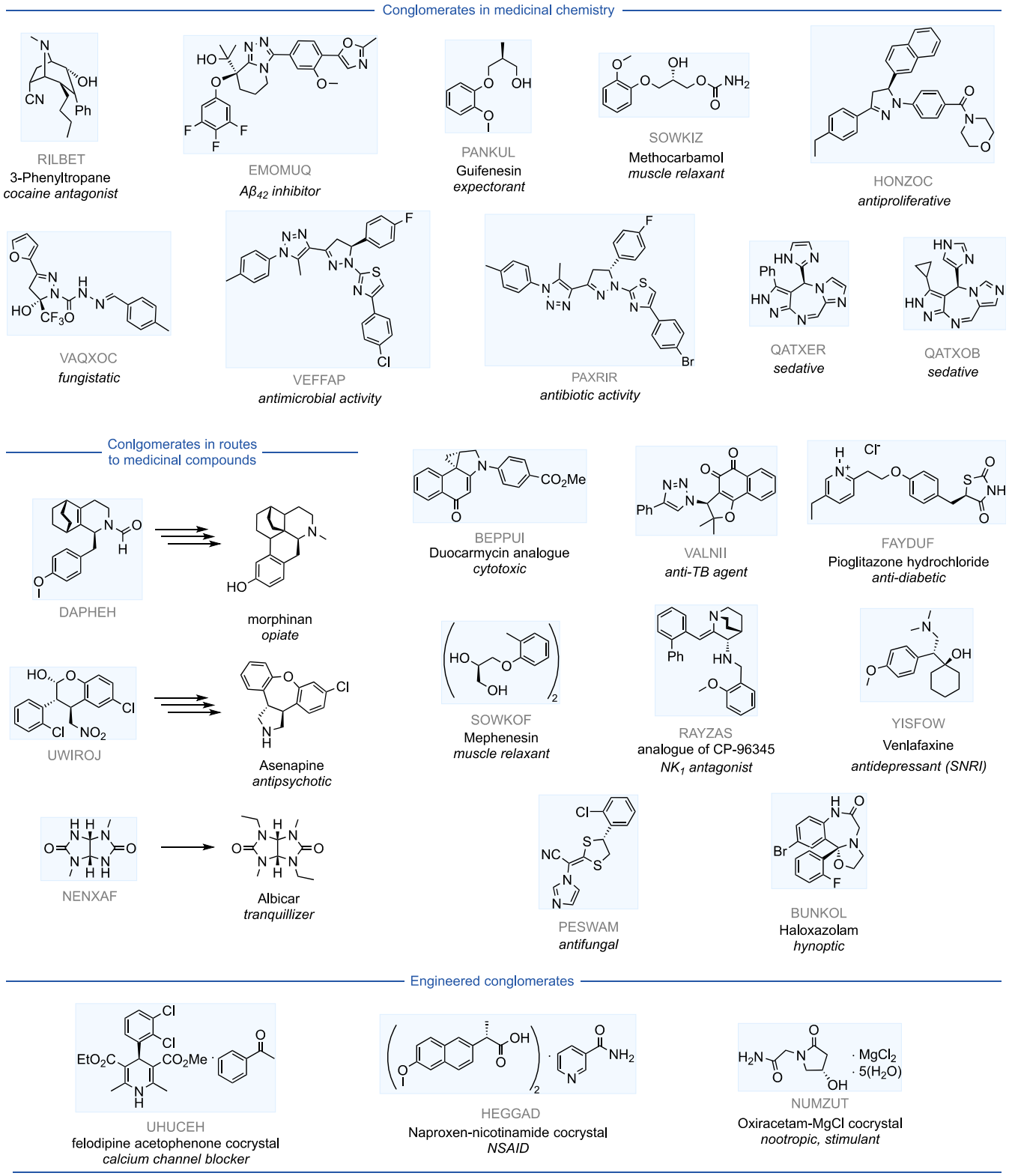


Figure 5. Conglomerate crystals present in medicinally relevant compounds

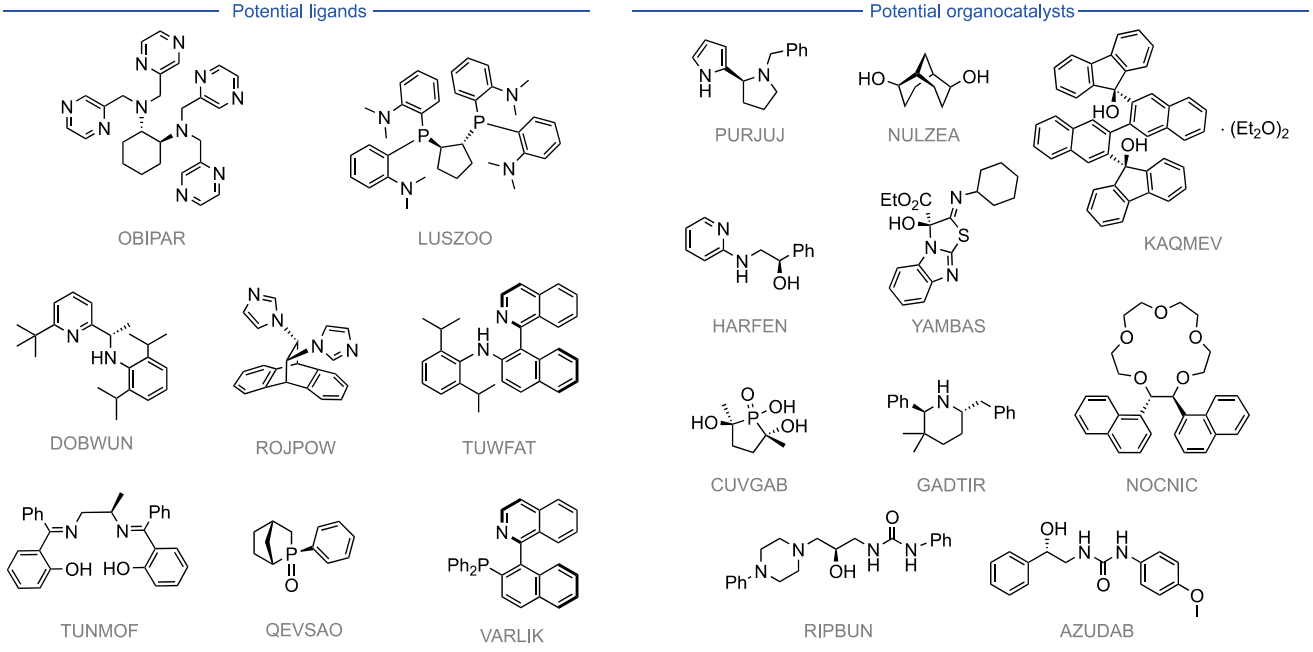


Figure 6. Potential ligands and organocatalysts from conglomerate crystals.

to incorporate a conglomerate based asymmetric synthesis or if a final target itself is reformulated to become conglomerate crystal. The choice of solvent has also been shown to control the formation of a conglomerate crystallisation over a racemic crystal.[71–73] The few cases of analysis of both racemic and conglomerate polymorphs of crystals are invaluable case studies for the development of methods to predict and understand conglomerate formation.[74,75] Cases in which a conglomerate crystal formed a racemic twin are also of interest in further understanding this phenomenon and has been collated in the *Supporting information*.

From surveying the full list of conglomerate crystals, it is possible to identify structures of interest. Structures with potentially broad applications as chiral ligands and organocatalysts are shown in **Figure 6**. This highlights the possibility of utilizing conglomerate crystallisation as a new chiral pool. Within this list are C_2 symmetrical pyrimidine (OBIPAR[76]), phosphine (LUSZOO[77]) and imidazole (ROJPOW[78]) ligands, an atropsiomeric quinoline (TUWFAT[79]), an α-methylpyridine (DOBWUN[80]), and a chiral salen ligand (TUNMOF[81]). Potential types of organocatalysts such as the C_2 symmetrical diol (NULZEA[82]), a PTC (phase transfer catalyst) crown ether (NOCNIC[83]), and chiral phosphoric acid (CUVGAB[84]), chiral ureas (RIPBUN,[85] AZUDAB[86]), benzotetramisole (YAMBAS[87]), amino-alcohol (HARFEN[88]), and imidazole (PURJUJ[89]) may also find use in asymmetric synthesis. These are only selected examples, and we would encourage the community to view our full list of structures they may deem useful to their research. Due to the diversity of scaffolds within the full list, we hope that it may become a new chiral pool, with synthetic groups using these structures as a means to access spontaneously enriched starting materials, products, ligands and catalysts.

We are aware that such a proposal is controversial amongst synthetic and crystallographic communities, and questions on its utility may arise:

Why should synthetic chemists care about a crystallographic phenomenon? It is a phenomenon that can directly affect the enantioenrichment of crystalline materials. If a recrystallisation had been performed as a purification step on a material which exhibited conglomerate behaviour, selection of a crystal from this material would not only give different diffraction properties in SCXRD and PXRD, but would also affect the recorded melting point, IR spectra, Raman spectra, and interactions with other enantioenriched species, such as those encountered in biological and pharmaceutical studies (IC_{50}, LD_{50}, protein binding, pharmacokinetics, pharmacodynamics).

How are conglomerate crystals synthetically useful? The curation of this list of conglomerates should not only aid future

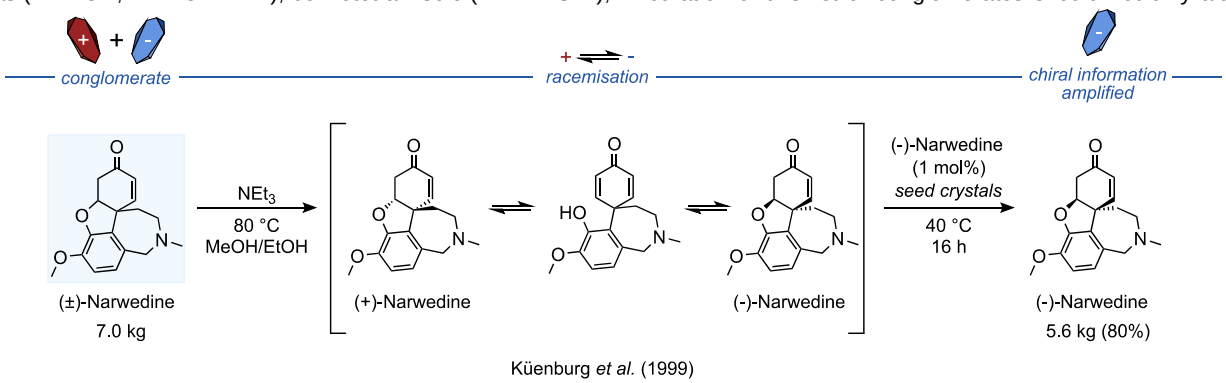


Figure 7. Pilot scale spontaneous deracemisation of Narwedine.

research on understanding this fundamental crystallisation phenomenon, but also acts as a potential source of chiral information for the synthetic community. By tracking materials which undergo this type of crystallisation, the possibility of creating general asymmetric routes to compounds by exploiting a powerful mode of chiral amplification can be achieved, whereby a substrate is able to bias its own enantioenrichment. The exciting synthetic potential of conglomerate crystals was demonstrated in the case of the natural product Narwedine.[90] **Figure 7** highlights the process that was developed on a pilot scale synthesis, showing this strategy in asymmetric synthesis can reliably produce desired enantioenriched materials in a cost effective manner for industrial syntheses.[91] Choosing a new substrate from this conglomerate list and finding the means to racemise the stereocentre(s) present in its structure will allow for the asymmetric synthesis of a compound without relying on the current biological chiral pool. This new chiral pool of conglomerate crystals contains a huge variety of structural diversity, with each one being a potential target for spontaneous asymmetric synthesis. A selection of candidates and their hypothesized deracemisation conditions are proposed within **Figure 8**. The challenge now rests on the synthetic chemists to view the structures in this list and use their creativity to develop conditions to exploit this source of chiral information.

Conclusion

A list of over 1,700 conglomerate crystals has been compiled from the CSD and literature, representing 41% of the predicted chiral conglomerate compounds contained within the CSD. Incentivising synthetic chemists to rapidly communicate their crystal structures with a description of the synthetic procedures and reagents which produced the material – even if such crystals are considered unremarkable by the crystallographic community or the synthesis unremarkable to the synthetic community – is the best method to create new conglomerate crystals and promote a greater integration of these communities. A simple change in the deposition process to the CSD, which could prompt the synthetic chemist/crystallographer to consider if the material originated from a racemic process, would avoid the need to conduct arduous manual searches in the future. We propose that this list of chiral conglomerates could be viewed as a potentially limitless, rapidly increasing, chiral pool; one which is not bound to biological sources. We hope that the curation of this list of conglomerate crystals aids the development of spontaneous asymmetric synthesis protocols and furthers the understanding in the formation of conglomerate crystal behaviour.

Experimental Section

The output of the *ConQuest* search in its unedited form is made available (.xlsx). The full manually curated list of conglomerate crystals along with their chemical structures and their associated references are available within *Supporting Information* (.pdf)

CSD version 5.41 (November 2019) was used for the search. Search queries were generated using *Conquest*, with the following queries chosen to try and minimise the total number of crystals to be checked while also maximising the potential number of conglomerate candidates. Crystals must exist in Sohncke space group *AND* Z′ = 1. Crystals must *NOT* be in carbohydrate, steroid, peptide

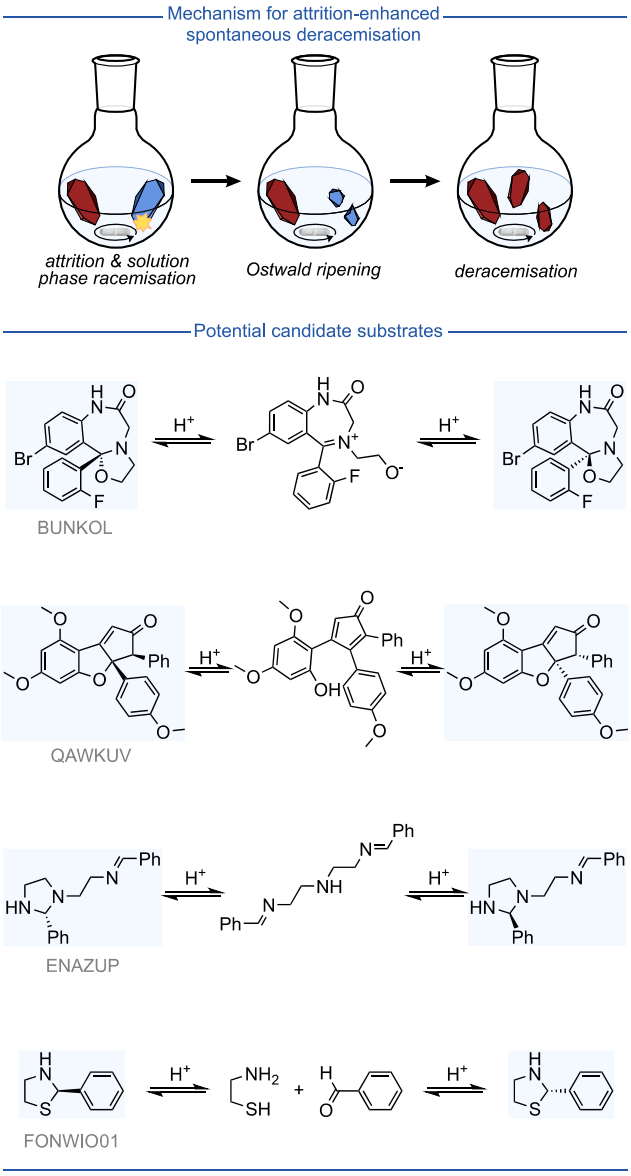


Figure 8. Mechanism of attrition-enhanced deracemisation and hypothesised candidates.

or nucleoside/nucleotide classes. Must have carbon centre with C(Non-metal)$_4$ *OR* H-C(Non-metal)$_3$. The main focus was put on carbon stereocentres since they make up 98% of all stereocentres within in the CSD. Crystals must be organic, no polymer, single crystal only, $R_1 < 0.075$, no errors. Disordered structures were allowed. It was also found that specific strings of text could be used to exclude certain natural products, including: “isolated”, “sourced from”, “extracted”, “bark”, “marine”, “sponge”, “penicillium”. Natural products could be further filtered when sorting the resulting CSD hits by their structure names; generic naming such as “cinchonine”, “strychnine”, “Striatin A” could be excluded due their natural sources or as targets for asymmetric total syntheses. This generated a list of 30,204 crystals as potential conglomerates. Compounds listed with known stereochemical assignments could be excluded from the list too. Compound names with the following: (+), (-), D, L, (R) and (S), were removed from the list as these were either sourced from the natural chiral pool or were produced from enantioselective methodologies and XRD was used for absolute configuration assignment. Leaving 21,098 crystals to be inspected manually. Likewise, compounds labelled as a racemate within their compound name, such as: *rac*, (±), and (D/L) were earmarked as potential conglomerate candidates for further checking.

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Conflict of Interests

The authors declare no conflicts of interest.

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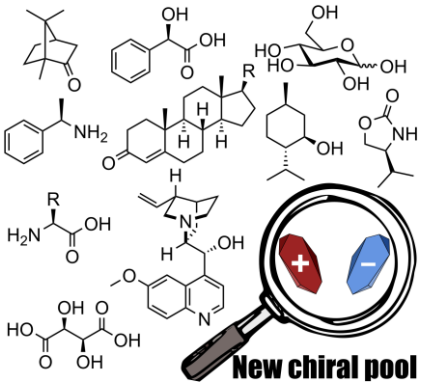
Entry for the Table of Contents



Hidden in plain sight! A search of the CSD has uncovered over 1,700 conglomerate crystals able to spontaneously enantioenrich themselves. This list is considered to be a new, potentially limitless chiral pool for synthetic chemists which is not linked to biological sources.

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